The Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by an Act of the Legislature of the Province of Ontario and reconstituted by The Cancer Act, 1957. The Cancer Act states that, "The object of the Foundation is to establish and conduct a program of research, diagnosis and treatment in cancer, including,

(a) the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or elsewhere;

(b) the transportation of patients and escorts to its treatment centres or to the hospital of the Institute for diagnosis, treatment or investigation;

(c) the establishment, maintenance and operation of hostels in connection with its treatment centres or the hospital of the Institute;

(d) the laboratory and clinical investigation of cancer problems;

(e) the co-ordination of facilities for treatment;

(f) the adequate reporting of cases and the recording and compilation of data;

(g) the education of the public in the importance of early recognition and treatment;

(h) the providing of facilities for undergraduate and postgraduate study;

(i) the training of technical personnel; and

(j) the providing and awarding of research fellowships."

Part II of The Cancer Act, dealing with The Ontario Cancer Institute, as amended by The Cancer Amendment Act, 1968-69, provides that the Institute Board shall consist of 15 persons appointed by the Lieutenant Governor in Council. Five members of the Institute Board shall be representatives of the Foundation, one of whom shall be the chairman of the Foundation. The Act specifies that one of the Foundation representatives on the Board of the Institute shall be the chairman of the Institute.

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Errata

OCTRF

CANCER IN ONTARIO 1987

Epidemiology and Statistics

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The attached Tables I-IV are provided to replace the tables (pages 183, 184, 186 and 187) which were incorrect. Please insert or attach these in your copy of *Cancer in Ontario* 1987.

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91-00694/

TABLE I

Annual Number of New Cases of Malignant Neoplasms in Males by Site of Disease and Age at Diagnosis, Ontario 1985 (Provisional Data*)

Revised August 1988

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral Cavity	140-145	1	0	0	3	2	5	5	10	16	24	46	83	80	66	59	98	8	506	9
Pharynx	146-148	0	0	0	2	1	1	3	8	13	12	18	22	35	21	19	17	0	172	
Esophagus	150	0	0	0	0	0	0	0	0	6	10	14	37	47	33	30	50	1	228	
Stomach	151	0	0	0	0	0	0	2	6	11	23	35	67	65	80	91	173	2	555	7
Intestine, excepi rectum	152, 153	0	0	1	0	1	4	10	19	27	62	112	203	277	311	325	548	4	1904	3
Rectum and anus	154	0	0	0	0	1	2	7	6	21	27	55	80	121	137	108	188	6	759	5
Pancreas	157	0	0	0	0	0	1	2	1	7	14	25	46	65	59	74	130	0	424	
Nasal cavities, middle ear and accessory sinuses	160	0	1	0	1	0	0	1	3	1	3	1	3	6	4	2	13	0	39	
Larynx	161	0	0	0	0	0	1	0	1	4	13	40	65	68	55	50	41	2	340	
Trachea, bronchus and lung	162	0	0	0	0	2	3	5	20	49	90	245	419	584	625	534	680	6	3262	1
Bone	170	0	1	9	7	5	2	2	5	3	2	2	1	9	5	5	13	1	72	
Connective tissue	171	0	1	4	2	4	9	9	3	8	9	9	16	17	14	7	20	0	132	
Malignant melanoma of skin	172	2	0	1	0	17	30	27	48	42	34	62	60	61	60	29	61	11	545	8
Prostate	185	1	0	0	0	0	0	0	1	2	13	49	132	324	493	614	1213	7	2849	2
Testis	186	1	1	1	13	41	36	48	38	13	13	11	7	2	1	1	5	0	232	
Bladder	188	0	1	0	2	3	6	5	11	18	37	97	128	184	196	213	372	0	1273	4
Kidney and other urinary	189	12	0	0	0	1	2	2	7	19	30	51	53	84	64	66	93	1	485	10
Brain and other nervous system	191, 192	16	9	9	9	13	12	20	16	29	21	24	52	58	36	27	40	0	391	
Thyroid gland	193	0	1	1	2	5	10	8	11	4	2	9	9	7	6	3	6	1	85	
Lymphosarcoma and reticulosarcoma	200	0	1	3	5	10	4	5	11	15	16	20	39	39	50	41	57	1	317	
Hodgkin's disease	201	0	4	3	22	23	24	19	11	8	8	5	14	5	7	9	6	1	169	
Other lymphomas	202	4	1	3	2	5	6	10	19	23	28	31	34	32	39	37	54	8	336	
Multiple myeloma	203	0	0	0	0	1	0	0	2	4	6	10	29	31	45	37	65	3	233	
Leukemia	204-208	30	14	7	18	11	8	11	14	13	14	36	46	51	71	86	158	3	591	6
Other and non-specific	Residual	15	4	5	6	17	8	15	33	37	74	100	155	252	224	201	421	7	1574	
TOTAL	140-208[3]	82	39	47	94	163	174	216	304	393	585	1107	1800	2504	2702	2668	4522	73	17473	

* See Text.
1 ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977
2 Rank order for 10 most common sites (or site groups).
3 Excluding non-melanotic skin cancers (ICD9 number 173)

TABLE II

Annual Number of New Cases of Malignant Neoplasms in Females by Site of Disease and Age at Diagnosis, Ontario 1985 (Provisional Data *)

Revised August 1988

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral Cavity	140-145	0	0	1	0	0	3	3	6	12	16	20	36	25	36	31	68	6	263	
Pharynx	146-148	0	0	0	0	0	0	1	2	3	1	7	11	5	11	8	13	0	62	
Esophagus	150	0	0	0	0	0	0	0	0	1	5	1	13	17	9	19	53	0	118	
Stomach	151	0	0	0	0	0	3	4	10	4	11	24	23	33	45	47	145	0	349	
Intestine, except rectum	152, 153	0	0	2	2	2	5	8	21	56	53	99	177	251	282	283	696	3	1940	2
Rectum and anus	154	0	0	0	0	0	1	7	7	13	14	35	48	74	104	77	223	5	608	7
Pancreas	157	0	0	0	0	0	0	1	4	4	9	13	34	36	66	49	159	0	375	
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	1	0	1	1	0	3	1	5	1	6	6	12	0	37	
Larynx	161	0	0	0	0	0	0	0	1	1	6	5	10	11	7	10	10	0	61	
Trachea, bronchus and lung	162	0	0	0	0	0	2	4	16	39	79	121	197	228	274	201	296	3	1460	3
Bone	170	0	2	7	6	1	4	1	2	1	1	0	2	1	4	2	12	0	46	
Connective tissue	171	0	2	2	5	3	4	5	4	6	11	5	10	11	8	7	27	0	110	
Malignant melanoma of skin	172	0	1	1	8	27	32	48	74	57	51	52	56	49	53	40	78	10	637	6
Breast	174	1	0	1	1	4	31	103	216	355	372	504	529	574	492	467	871	20	4541	1
Cervix uteri	180	0	0	0	1	7	40	74	84	57	39	46	51	52	38	25	44	3	561[4]	8
Body of Uterus	182	0	0	0	0	0	1	6	18	24	47	101	157	216	169	145	155	2	1041	4
Other and unspecified uterus	179, 181	0	0	0	1	1	1	1	0	3	10	4	6	9	2	5	15	1	59	
Ovary and fallopian tube	183	1	1	1	4	6	15	13	27	25	51	60	86	111	94	78	120	1	694	5
Bladder	188	1	0	0	1	0	3	2	7	6	11	22	41	51	56	61	177	1	440	10
Kidney and other urinary	189	7	1	1	0	0	0	1	6	13	17	19	39	48	52	37	77	2	320	
Brain and other nervous system	191, 192	11	4	9	9	11	8	4	14	14	11	32	29	38	33	35	47	0	309	
Thyroid gland	193	0	0	2	9	16	30	34	25	25	16	21	28	23	19	13	21	0	282	
Lymphosarcoma and reticulosarcoma	200	0	0	1	1	1	2	5	4	9	11	13	28	28	38	29	76	1	247	
Hodgkin's disease	201	0	1	5	18	25	17	12	9	3	2	6	4	6	5	5	9	3	130	
Other lymphomas	202	1	0	1	4	4	5	6	8	16	21	14	26	45	51	37	70	3	312	
Multiple myeloma	203	0	0	0	0	0	0	0	1	1	4	12	19	26	31	44	87	5	230	
Leukemia	204-208	21	13	16	4	5	8	7	13	15	11	13	29	48	40	52	158	3	456	9
Other and non-specific	Residual	11	2	1	3	7	18	24	16	35	44	71	116	172	145	196	519	6	1386	
TOTAL	140-208[3]	54	27	51	77	121	233	375	596	798	927	1321	1810	2189	2170	2009	4238	78	17074	

* See Text.
[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2] Rank order for 10 most common sites (or site groups).
[3] Excluding non-melanotic skin cancers (ICD9 number 173).
[4] Approximately 10% non-invasive cancer of the cervix.

TABLE III

Adjusted Rates[1] and Cumulative Risks (age 0-74)[2] Incidence (I) and Mortality (M) from Malignant Neoplasms in Males, by Site and Age, Ontario 1985

Revised August 1988

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral Cavity	140-145	I	0.1	0.9	3.3	20.3	43.9	71.0	9.3	1.07
		M	0.0	0.1	0.3	5.6	12.2	28.9	2.6	0.29
Pharynx	146-148	I	0.0	0.4	2.6	7.1	16.1	12.3	3.3	0.39
		M	0.0	0.1	0.8	3.0	7.8	7.3	1.5	0.18
Esophagus	150	I	0.0	0.0	0.7	8.0	23.6	35.5	4.2	0.50
		M	0.0	0.0	0.9	9.1	27.3	43.9	4.9	0.60
Stomach	151	I	0.0	0.0	2.0	16.7	49.8	123.9	9.8	1.12
		M	0.0	0.2	1.2	9.5	41.2	126.4	7.9	0.84
Intestine, except rectum	152, 153	I	0.1	0.4	5.9	50.2	193.6	390.9	34.0	3.97
		M	0.0	0.1	2.5	18.5	75.5	229.1	14.6	1.60
Rectum and anus	154	I	0.0	0.2	3.7	21.7	78.4	132.6	13.7	1.62
		M	0.0	0.0	0.9	5.7	25.0	85.8	5.0	0.52
Pancreas	157	I	0.0	0.1	1.1	11.3	41.8	96.0	7.6	0.88
		M	0.0	0.1	1.7	10.0	45.7	113.1	8.2	0.94
Larynx	161	I	0.0	0.1	0.6	15.5	37.0	28.9	6.4	0.83
		M	0.0	0.0	0.2	3.7	12.5	16.9	2.1	0.27
Trachea, bronchus and lung	162	I	0.0	0.4	8.1	99.3	372.5	481.2	59.6	7.34
		M	0.0	0.2	5.1	76.6	321.3	558.2	52.5	6.29
Bone	170	I	0.9	1.2	1.0	0.7	4.1	9.7	1.4	0.12
		M	0.1	0.8	0.2	0.1	1.1	2.6	0.4	0.03
Malignant melanoma of skin	172	I	0.3	3.7	11.9	21.5	32.7	44.8	10.2	1.05
		M	0.0	0.2	2.3	4.0	10.3	18.2	2.4	0.25
Prostate	185	I	0.1	0.0	0.3	24.7	300.0	898.7	48.8	5.38
		M	0.0	0.0	0.0	4.0	72.3	402.0	15.2	1.34
Testis	186	I	0.3	7.3	9.5	4.5	0.9	4.0	4.5	0.34
		M	0.0	0.3	0.8	0.3	1.1	1.3	0.4	0.04
Bladder	188	I	0.1	0.9	3.6	35.1	125.6	273.2	22.9	2.63
		M	0.0	0.0	0.2	4.0	26.5	113.6	5.3	0.53
Kidney and other urinary	189	I	1.4	0.2	3.1	18.5	45.6	66.2	9.3	1.06
		M	0.1	0.1	1.2	7.1	17.4	38.2	3.7	0.43
Brain and other nervous system	191, 192	I	3.7	2.8	6.7	13.0	26.1	28.1	7.9	0.79
		M	0.7	1.5	2.8	8.0	21.8	17.0	4.6	0.54
Thyroid gland	193	I	0.2	1.4	2.2	2.7	3.5	4.4	1.6	0.15
		M	0.0	0.0	0.0	0.4	0.8	4.2	0.2	0.02
Lymphosarcoma and reticulosarcoma	200	I	0.4	1.6	3.3	10.1	27.8	38.7	5.9	0.68
		M	0.1	0.3	0.5	1.2	5.6	14.7	1.2	0.12
Hodgkin's disease	201	I	0.7	5.9	3.7	3.7	4.4	3.9	3.4	0.29
		M	0.0	0.9	0.7	0.8	3.4	2.3	0.8	0.09
Other lymphomas	202	I	0.9	1.1	5.4	13.1	23.0	38.5	6.3	0.68
		M	0.2	0.7	1.4	6.9	17.7	33.5	3.8	0.44
Multiple myeloma	203	I	0.0	0.1	0.7	5.8	24.1	48.6	4.2	0.50
		M	0.0	0.0	0.5	2.4	13.9	31.2	2.3	0.28
Leukemia	204-208	I	5.7	3.3	3.9	12.9	43.7	114.7	11.4	1.12
		M	1.0	1.6	2.6	6.7	28.1	93.5	6.6	0.67
TOTAL	140-208[4]	I	18.0	35.7	94.5	467.0	1673.7	3280.6	317.8	30.64
		M	2.6	8.0	29.8	211.7	875.5	2227.4	163.3	16.81

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.
[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research of Cancer (IARC) Scientific Publication No. 15, pp. 443-52, 1976).
[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

TABLE IV

Age-Adjusted Rates[1] and Cumulative Risks (age 0-74)[2] Incidence (I) and Mortality (M) from Malignant Neoplasms in Females, by Site and Age, Ontario 1985

Revised August 1988

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS) 0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral Cavity	140-145	I	0.1	0.2	2.2	9.6	16.5	27.8	4.0	0.45
		M	0.0	0.0	0.3	2.7	4.2	13.6	1.1	0.11
Pharynx	146-148	I	0.0	0.0	0.6	2.4	4.3	5.5	1.0	0.12
		M	0.1	0.0	0.0	1.6	1.8	2.7	0.5	0.05
Esophagus	150	I	0.0	0.0	0.1	2.5	7.9	20.8	1.5	0.17
		M	0.0	0.0	0.0	0.9	6.4	23.3	1.2	0.12
Stomach	151	I	0.0	0.2	1.8	7.9	22.1	57.6	4.7	0.51
		M	0.0	0.0	0.6	4.2	15.9	55.0	3.3	0.35
Intestine, except rectum	152, 153	I	0.2	0.8	9.3	43.2	145.6	280.4	27.1	3.12
		M	0.0	0.1	2.2	14.4	51.5	165.0	10.5	1.11
Rectum and anus	154	I	0.0	0.1	2.8	12.8	46.0	89.2	8.4	0.97
		M	0.0	0.0	0.5	3.8	13.4	44.2	2.8	0.29
Pancreas	157	I	0.0	0.0	0.9	7.2	27.1	63.9	5.0	0.57
		M	0.0	0.0	0.9	8.0	31.8	72.8	5.7	0.67
Larynx	161	I	0.0	0.0	0.2	2.9	5.0	4.0	1.0	0.13
		M	0.0	0.0	0.1	0.3	2.2	2.3	0.3	0.04
Trachea, bronchus and lung	162	I	0.0	0.2	6.4	53.0	127.4	121.4	23.0	2.87
		M	0.0	0.1	5.8	37.4	116.0	122.9	19.6	2.48
Bone	170	I	0.9	1.0	0.4	0.4	1.3	4.5	0.9	0.06
		M	0.3	0.1	0.0	0.1	0.5	1.5	0.2	0.02
Malignant melanoma of skin	172	I	0.2	5.4	17.8	22.3	25.8	31.7	10.9	1.08
		M	0.0	0.2	2.0	3.2	3.8	9.3	1.4	0.14
Breast	174	I	0.2	2.9	71.0	194.4	276.7	353.2	74.7	8.01
		M	0.0	0.4	12.9	55.3	112.9	184.1	24.6	2.79
Cervix uteri	180	I	0.0	3.8	21.0	18.9	21.2	18.2	9.8	0.97
		M	0.0	0.6	3.3	6.1	11.0	13.9	2.9	0.32
Other uterus	179, 181, 182	I	0.0	0.3	5.5	43.1	99.3	68.6	17.9	2.25
		M	0.0	0.0	0.3	3.1	13.6	34.7	2.4	0.27
Ovary and other uterine adnexa	183	I	0.3	2.1	6.6	26.9	51.5	48.5	11.4	1.32
		M	0.1	0.4	2.9	13.3	36.3	51.2	6.9	0.84
Bladder	188	I	0.1	0.3	1.5	9.7	29.9	70.8	6.0	0.66
		M	0.0	0.0	0.0	1.5	5.2	31.7	1.3	0.11
Kidney and other urinary	189	I	1.1	0.0	2.2	10.0	24.9	31.7	5.1	0.59
		M	0.3	0.3	0.2	2.2	10.0	22.6	1.9	0.21
Brain and other nervous system	191, 192	I	2.7	2.4	3.3	9.7	19.0	18.9	5.6	0.57
		M	0.4	0.9	1.9	6.9	15.6	15.3	3.5	0.40
Thyroid gland	193	I	0.2	4.5	8.3	8.9	10.1	8.3	5.1	0.48
		M	0.0	0.0	0.0	0.6	1.7	5.7	0.4	0.04
Lymphosarcoma and reticulosarcoma	200	I	0.1	0.3	1.9	6.9	17.1	31.1	3.7	0.41
		M	0.2	0.0	0.0	1.2	3.3	12.1	0.8	0.08
Hodgkin's disease	201	I	0.6	5.2	2.2	1.7	2.9	3.6	2.5	0.19
		M	0.0	0.2	0.2	0.7	1.8	1.7	0.4	0.05
Other lymphomas	202	I	0.2	1.1	3.2	8.5	24.2	28.1	4.9	0.57
		M	0.2	0.1	0.8	3.5	13.3	30.3	2.6	0.29
Multiple myeloma	203	I	0.0	0.0	0.2	4.6	17.6	34.8	3.0	0.37
		M	0.0	0.0	0.2	2.8	10.9	28.3	2.0	0.24
Leukemia	204-208	I	5.5	1.4	3.6	7.0	24.8	63.4	7.3	0.66
		M	1.2	1.4	2.6	4.6	15.6	49.7	4.3	0.40
TOTAL	140-208[4]	I	14.5	35.8	182.4	550.0	1145.8	1710.4	266.1	25.88
		M	3.3	5.3	41.2	198.6	559.6	1170.4	113.3	12.10

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.
[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research of Cancer (IARC) Scientific Publication No. 15. pp. 443-52. 1976).
[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

CANCER IN ONTARIO 1987

Biological Response Modifiers

The Cover

R*esponse modifiers influence biological systems through diverse mechanisms which include cellular activation, amplification of cell number or function, and modification of growth and differentiation. In the cover illustration, the response modifier (white ball) is released into a group of previously inactive components (red balls), thereby initiating their entry "into play". The impact of interaction is of great interest but is largely unknown (background of darkness), thus reflecting the clinical enthusiasm surrounding response modifiers despite the paucity of information on their clinical role and their effects upon the complex regulatory network upon which they impinge.*

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MESSAGE FROM THE CHAIRMAN

Photo: Tony V. Hauser

Each year brings challenges to the Foundation. 1987 was no exception.

The relocation of the London Centre was substantially completed and is scheduled to open in the Spring of 1988. Construction has started for the Northeastern Ontario Centre in Sudbury. Planning for expanded centres in Hamilton and Ottawa was completed and a beginning made for an expansion of the Toronto-Bayview Centre.

To fund these capital projects with the Ministry of Health, we continued to organize the Ontario Cancer Care Fund – a joint venture with Ontario Cancer Institute (OCI) and the Canadian Cancer Society Ontario Division. The aim is to raise 50 million dollars to be shared with the OCI. We are grateful that the Hon. William Davis has agreed to act as the Chairman of the Fund and Mr. William James as the President.

Because of other pressures, merger discussions with the OCI to form an "Ontario Cancer Agency" were discontinued in 1987, but those will be reactivated in 1988.

I am pleased to record the appointment to the Board in 1987 of Mr. K.R. Clarke, Chairman of the OCI, Ms. M.M. Conroy, Mrs. S. Geller, Rev. W.K. Jaggs, Ms. L. Kushnir, Ms. L. Sabourin and Mr. D.B. Webber. During 1987, Mr. G. Adams, Mr. G. Eligh and Dr. G.D. Hurteau were reappointed. In early 1988, Mr. G. Genchi and Mr. R. Potter, President of the Canadian Cancer Society Ontario Division will be appointed to the Board and Dr. J.Y.K. Wong will be reappointed. During 1987, the terms of the Hon. R.A. Bell and Ms. I. Rubin came to an end. I wish to welcome the new Members and thank those continuing or retiring for their commitment to the cause of cancer patients.

In closing, may I thank the Government of Ontario, the Canadian Cancer Society Ontario Division, the staff of the Regional Cancer Centres and the Head Office for their support in making the Foundation a growing, concerned and vibrant organization, bringing cure and care to cancer patients throughout Ontario.

Michael A. Meighen, Q.C.
Chairman

EXECUTIVE DIRECTOR REPORTS

In 1987, the Foundation continued its growth in numbers of patients, in staff, in programs and in space.

Largely because our people are growing older the incidence of cancer continues to rise – a change that is reflected in the increasing numbers of patients referred to our Regional Cancer Centres. Early returns suggest that, during the year 1987, new cases (malignant and benign) seen in our Centres rose to 17,000 – a 5% increase over 1986. Service visits rose to 499,000 – a 2% increase. To meet these demands and improve our services, we have increased our full-time and part-time staff, which now number 1175 – an 11% increase over 1986. Increased patient loads have placed major strains on our facilities; as the Chairman tells us in his message, these are being expanded.

In 1987 the Northeastern Ontario Oncology Program in Sudbury continued to evolve under the leadership of Dr. R.E.T. Corringham. It is not easy to break new ground but each of us admires the pioneer. The Program will have developed into a full Centre by approximately 1989-90.

To achieve effective cancer control in Ontario, the Foundation has striven to develop new programs in prevention, delivery of care, education and research. Elsewhere in this issue of *Cancer in Ontario* 1987 others have reported on education and research.

Of special note are two new programs that are in the process of development. With the leadership of Dr. E.A. Clarke, a proposal has been developed to establish an organized breast screening program under the auspices of the Foundation. This will be submitted to the Ministry of Health for funding in early 1988. We estimate that, in Ontario, this program will save more than 300 lives per year from breast cancer.

To bring cancer care closer to the patient's home and to reduce the pressure on the Centres, we are developing, under the leadership of Drs. W.H. Hryniuk and J.D. Gowing, a proposal for a system of community cancer clinics "networked" to our Centres. This proposal will be submitted to the Ministry of Health in 1988.

Because the Foundation is becoming an increasingly complex organization, we have taken steps to strengthen the Head Office staff. Thus we welcome Mr. Jerome Porat as Internal Auditor, and Ms Loraine MacLean as Manager of Human Resources. We are developing ways and means to improve our planning (capital and programs), our health economics and our effectiveness in public relations activities.

The Foundation interfaces with many organizations but an exceedingly important ally is the Canadian Cancer Society Ontario Division. We welcome Ms Dorothy Lamont as the new Executive Director of the Division and have begun to

improve liaison so as to address the major financial challenges we and the Society will face together during the next decade.

I wish to thank the Directors of the eight Regional Cancer Centres, their staffs and the staff of Head Office for their understanding and loyal support in coping with growing demands in a time of increasing economic constraints.

Finally, I must thank the people of Ontario who, through their Government, support our work. They are assisted, in no small measure, by the Canadian Cancer Society Ontario Division and by the spontaneous financial contributions of our patients, their families and their friends.

J. William Meakin, M.D.,C.M., F.R.C.P.(C)
Executive Director

No annual financial statement is included in *Cancer in Ontario* but a copy of such statement will be provided upon request to the Head Office of the Foundation.

OBITUARIES

Photo by Karsh

Dr. W. Gerald Cosbie
1894-1987

Dr. W.G. Cosbie died peacefully in West Vancouver on April 22, 1987, at the age of 93.

Dr. Cosbie was born in Toronto on January 29, 1894 and was educated at Upper Canada College and the University of Toronto Medical School. After graduation in 1915, he joined the Royal Canadian Army Medical Corps. Serving with the Third Canadian Division, he was wounded at Vimy Ridge; later he returned to his field ambulance and was awarded the Military Cross for outstanding bravery.

On his return to Canada in 1919, he undertook graduate studies and became Fellow of the Royal College of Surgeons of Canada, and Fellow of the Royal College of Obstetricians and Gynecologists. He pioneered and refined certain treatments for gynecological cancer and, on September 13, 1921, looked after the first patients who were treated by radiotherapy in Toronto General Hospital (TGH).

At the time of death of Dr. Gordon Richards in 1949, Dr. Cosbie was gynecological consultant at the Ontario Institute of Radiotherapy at the TGH. In spite of a busy practice, heavy lecturing and clinical commitments at the University of Toronto and the TGH, Dr. Cosbie stepped in to fill the void left by Dr. Richards; Dr. Cosbie succeeded him as a member of the Foundation, as Chairman of the Advisory Medical Board and its Executive Committee thus giving it vigorous guidance. He also played an important role in discussions with the provincial government which led to the establishment of the Ontario Cancer Institute.

On his retirement from the active university staff in 1954, Dr. Cosbie accepted, on a part-time basis, the post of Medical Director of the Foundation; unofficially, he had been performing these duties since 1949. Later, on his retirement from private practice, he became full-time Medical Director.

In 1957, Dr. Cosbie became Vice-chairman of the Foundation, a post he held until 1971. During this period he gave great support to the Foundation chairmen.

On June 30, 1965, Dr. Cosbie resigned as Medical Director. Under his vigorous and able leadership, many new programs had been introduced and existing programs improved and expanded. He was an entertaining raconteur, a fluent speaker and a skilled writer, making him an excellent representative of the Foundation and strong exponent of his work. In 1973, on moving to Vancouver, Dr. Cosbie resigned from the Board after serving the Foundation and the Advisory Medical Board committees for many years.

In 1976, the Foundation established a lectureship in honor of Dr. Cosbie. The first such lecture, which was awarded to the newly-formed Canadian Oncology Society, was delivered on January 27, 1977 in Toronto by Mr. Basil Morson, the distinguished pathologist of St. Mark's Hospital in London (U.K.). Fortunately Dr. Cosbie was able to be present.

Dr. Cosbie will be fondly remembered by all who were associated with him.

Dr. T.A. (Sandy) Watson
1914-1987

It is with deep sadness that we report the death on April 17, 1987, at age 73, of Dr. Thomas Alexander Watson. Affectionately known as "Sandy", he was a dedicated and respected director at the London Regional Cancer Cancer from May 1963 to his retirement in June 1980.

Born in New Zealand, of British parents, Dr. Watson graduated from medical school in 1937. He won numerous qualifications and held positions in China, London (U.K.), Manchester and Liverpool, arriving in Canada in 1946 to become Director of the Saskatoon Cancer Clinic. He served with distinction in many societies and committees in North America and was honored by the Universities of Saskatchewan, McGill, Western Ontario, Dalhousie, Liverpool, and by the Royal College of Physicians and Surgeons.

Wherever he served it was evident that quality patient care was uppermost in his mind. While director of the London Regional Cancer Centre, he succeeded in winning installation of the Betatron in 1965, expansion in such facilities as treatment units, the lodge, growth of chemotherapy treatment and a vast increase in the number of staff.

Dr. Watson was one of the great pioneers in radiation therapy, yet he made contributions to other aspects of oncology at provincial and national levels.

On March 29, 1949, in Saskatoon, Dr. Watson was the first Canadian to treat a patient with the Betatron.

Dr. Watson will be remembered by his friends, acquaintances and co-workers as a dedicated, caring man.

EDUCATION

SUMMARY OF OCTRF EDUCATION ACTIVITIES

The Foundation is reviewing those professional and public education activities which emanate from the Regional Cancer Centres and from Head Office. This review will form the background for a new plan for the Foundation's education activities. The professional education programs for 1987 were as follows.

Postgraduate Medical Education

Postgraduate medical education was supported in 1987 through the funding of a minimum of 15 residency posts in oncology (medical or radiation) at an annual cost of approximately $500,000. These residency posts, which are supplementary to those funded by the Ministry of Health in the Province's five medical schools, are an attempt to relieve the serious manpower shortage in these specialties.

Undergraduate Medical Education

Ivan H. Smith Memorial Studentships

This program, jointly funded by the Canadian Cancer Society Ontario Division and the Foundation, provided 18 studentships for periods of from 4 to 12 weeks. Competition for the studentships is open to medical students after their second year of study. Working at the regional cancer centres and the Princess Margaret Hospital, the Ivan H. Smith students are introduced to the many rewarding aspects of a career in oncology. In 1987, all studentships were taken outside of the academic year, except for one elective. Participating centres were: Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview, Windsor, and the Princess Margaret Hospital.

The Harold E. Johns Summer Studentships in Medical Physics

In 1987, 12 studentships were undertaken in the following centres: Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview, and the Princess Margaret Hospital. This program, which is intended to stimulate the entry of medical physicists into oncology, is funded from a special cancer services improvement grant from the Canadian Cancer Society Ontario Division.

Continuing Medical Education

In 1987, the regional cancer centres and the Princess Margaret Hospital conducted active programs for continuing education through clinic days, seminars, guest lectures, and lectures in the community by staff members.

The "phone-in" cancer information service, a pilot project sponsored by the

Foundation and the Canadian Cancer Society Ontario Division, was expanded province-wide in 1987.

On October 23, 1987, Dr. Alon Dembo, Associate Professor, University of Toronto, delivered the Vail Lecture at the Skyline Hotel, Ottawa, during a gynecologic oncology meeting arranged by the University of Ottawa's Department of Obstetrics and Gynecology. Dr. Dembo's topic was "Update and New Directions in the Treatment of Choriocarcinoma".

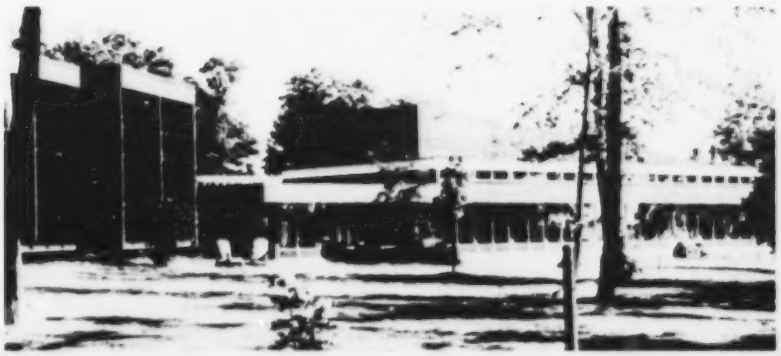
In September 1987, during the Annual Meeting of the Canadian Oncology Society in Winnipeg, Manitoba, Dr. David Schottenfeld, Chairman of the Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, delivered the W.G. Cosbie Lecture. His subject was "Interactions of Nature and Nurture in the Pathogenesis of Human Cancers".

Dr. Yigal Barak, Head of Hematology Section, Pediatric Research Institute, Kaplan Hospital, Rehovot, Israel, was the 1987 exchange visitor selected under the Joseph J. Schiffer Exchange Program. This program, sponsored jointly by Mount Sinai Hospital and the Foundation, promotes scientific interchange between Israel and the Toronto Health Sciences Centre by providing support on an annual basis for exchange visits (in alternate years) of individuals working in cancer treatment and/or research.

Two Ontario Cancer Foundation Lectures were awarded in 1987. On June 19, at a meeting of the Network of Social Workers in Oncology held at the Toronto General Hospital, Dr. David Wellisch, Psychologist from U.C.L.A., spoke on "The Chronic Hold Pattern: Cancer Patients and Their Families". In September, at the Annual Convention of the Association of Pathologists held in Toronto, selected speakers addressed the past, present and future of pathology and laboratory medicine as related to oncology.

J.C. Laidlaw, M.D.
Mary Lou Erochko

11TH CLINICAL CANCER RESEARCH CONFERENCE



Geneva Park — Site of the
11th Clinical Cancer Research Conference

On September 28-30, 1987, the 11th Clinical Cancer Research Conference was held at Geneva Park near Orillia, Ontario, where these meetings have been held since 1967. This site provides an excellent setting for informal discussion of cancer problems among 225 staff and guests, who were in attendance.

The theme of the 1987 conference was "Biological Response Modifiers". Drs. Simon Sutcliffe and Ian Quirt of the Ontario Cancer Institute arranged the program and the faculty included several distinguished speakers from outside the province. Dr. Samuel Saks of Genentech, South San Francisco, presented the OCTRF Research Lecture, and following this lecture, participated in the panel discussion. Others included Drs. D. Chapman, Cross Cancer Institute; A.A. Gottlieb, Imreg, Inc., New Orleans; J. Munzenrider, Massachusetts General Hospital; and H.S. Grossberg, Schering-Plough Corp., Kenilworth, N.J.

Staff members of the OCTRF Regional Cancer Centres and representatives from the health science centres participated in a poster session, which outlined some of the research projects being undertaken in these institutions. The authors were present on Tuesday afternoon to answer questions about their work.

In addition to the scientific posters, there were special exhibits to illustrate some of the Foundation's current activities. Mrs. Barbara Rigby of the Hamilton Regional Cancer Centre gave information about the Cancer Information Service, which is jointly funded by the Foundation and the Canadian Cancer Society Ontario Division. Dr. P. McCulloch and members of the Ontario Clinical Oncology Group presented up-to-date information about this program and its future plans. Mrs. June Murphy, manager of Information Systems, and members of her staff demonstrated a system for online inquiry using the Ontario Cancer Registry Data Base.

In the final session, a small group led by Dr. L. Siminovitch discussed the Foundation's research policy for the 1990s. Dr. Siminovitch noted that the Foundation is most anxious to develop "a critical mass" of research workers associated with the regional cancer centres, which would involve groups of investigators from affiliated hospitals and universities. These groups would be in geographical conginuity. Hopefully, these groups could provide a continuum of research from bench to bedside to community. To accomplish this, the Foundation recognizes that, in addition to supporting career scientists, it will be desirable to recruit clinician scientists (including physicists), whose disciplines may extend from molecular genetics to clinical epidemiology to behavioral sciences.

COUCHICHING CONFERENCE 1987

MEMBERS OF THE BOARD AND HEAD OFFICE
Mr. R. D. Gray, Mrs. Betty Johnson, Dr. G. R. Walker,
Ms. Lorri Kushnir and Dr. J. W. Meakin

GUEST SPEAKERS
Drs. J. D. Chapman, J. E. Munzenrider,
S. Saks and A. A. Gottlieb

CENTRE DIRECTORS
Drs. G. C. K. Mok, G. E. Catton, R. E. T. Corringham,
W. M. Hryniuk and A. D. Ginsburg

HONOURABLE OLD TIMERS
Mr. J. H. Broughton, Drs. J. E. Maus,
R. C. Burr and H. E. Johns

EDITORIAL: BIOLOGICAL RESPONSE MODIFIERS IN CLINICAL ONCOLOGY

The concept of an immunoregulatory network that might be stimulated to reject cancer cells is an attractive concept and, given the expanding knowledge of cellular immunology and the availability of pure, characterized mediators of the immune response, it seems increasingly amenable to investigation.

A number of such mediators – lymphokines or cytokines – which have been described, appear to subserve these major functions:

- activation of effector cells, e.g., interleukin-1;
- amplication of effector-cell number or function, e.g., interleukin-2, Imreg-1;
- effector-cell differentiation, e.g., T-cell differentiation factors, B-cell growth factors.

By implication, therefore, the immune system is both endocrine and autocrine, being self-regulatory through products expressed under differing conditions of activation and acting through specific receptors expressed on the cell surface.

The concept that modulation of immune function by exogenous mediators might be beneficial in cancer is based upon the following tenets:

- immunological function is aberrant in cancer;
- the degree of aberrant immunological function, tumor growth and disease progression are correlated;
- that regulation of immune function to the "norm" would be associated with apparent clinical benefit in terms of tumor control.

To what extent are these tenets true?

Firstly, is immunodeficiency relevant in the context of clinical cancer? It is well-recognized that certain genetically-determined immunodeficiency states, e.g. Wiskett-Aldrich syndrome – ataxia-telangiectasia, are associated with the subsequent development of cancer. Acquired immunodeficiency, either HIV-associated or through therapeutic immunosuppression, also is associated with the development of cancer. In genetically-determined immunodeficiency, the new growths most commonly observed are malignant lymphomas while, in HIV-acquired immunodeficiency, we see Kaposi's sarcoma and less frequently malignant lymphoma. Tumor regression has been noted to accompany cessation of therapeutic immunosuppression. These observations, which support the concept of "immunological surveillance", have promoted the belief that the immunodeficiency state plays a role in cancer, either casually or in association, and that one might modify the natural history of maligancy through alteration of immune status.

Secondly, does an immunodeficiency state exist in cancer, and does it correlate with the natural history of the disease? Certain malignancies, e.g.

Hodgkin's disease, are associated with aberrant cell-mediated immunity. In this rather unique circumstance, there is some suggestion that the extent of immunodeficiency parallels the natural history of the disease, however this issue is confounded by effects of treatment on immune function. In addition, abnormal in vitro immune function is not reversed by successful therapy – again, however, there is the conflicting role of therapy.

In vitro parameters of cell-mediated immune function also are abnormal in advanced solid maligancies. However, there is little indication of abnormal cell-mediated immune response in patients with early, localized untreated solid cancer. Not only is there no readily characterizable defect, but, where demonstrable, the immunological abnormalities reveal no common pattern from malignancy to malignancy. It is not clear whether the absence of a common pattern of immunodeficiency in cancer reflects the insignificance of immune competence or whether there exists an error in the choice of parameters of their methods of measurement.

Finally, is there a precedent for believing that immunomanipulation may influence the natural history of cancer? Some early reports indicate that, when transplanted at the time of organ donation in immunosuppressed recipients, allogeneic tumor became engrafted and grew rapidly. Similarly, in transplantation settings, discontinuation of immunosuppression has been associated with reject or regression of allogeneic and autologous tumor. the original anecdotal observations regarding tumor response following transfer factor, BCG, etc., have been demonstrated more formally in studies using interferon and, more recently, LAK cells with interleukin-2. These studies clearly indicate an effect, although the mode of action, dose-response relationship and reproducibility of observations remain imprecise.

In this mileau of optimism based upon: (1) clear demonstration of biological activity; (2) recognized limits of conventional therapy; (3) desire for "natural" mechanisms for regulation of cancer; and (4) ready availability of lymphokines through recombinant technology, clinical studies are being proposed for combinations of lymphokines, and for combinations of cytotoxic drugs/radiation and immunoregulators. These studies should bear on the following issues, which are central to the understanding of lymphokine activity:

- Should not we understand the physiological role of the modulator in the normal immune response before we attempt to assess its action in the abnormal physiology of cancer?
- Rarely has the definition of immunodeficiency been characterized before immunomanipulation. Have we clearly defined the abnormal immune response to be modified?
- Selection processes for patient entry into immunoregulation studies commonly involve the type of tumor and the response to previous therapy. Given no apparent consistency of immunological deficit within tumor type or by response to previous therapy, selection by these criteria is empiric. It

might be more sensible to select according to the nature of the immune deficit as defined by clinical or in vitro parameters.

- What is the end-point of the intervention? Should be consider a positive result to be a change in immunological function towards the "norm"? Is it reasonable to report tumor response in the absence of measured immunological parameters? Is it reasonable to judge an immunological response modifier by the criteria of tumor response, duration of remission and survival?
- Is the mechanism of action of the immunoregulatory agent understood? It is clear that lymphokines encompass the spectrum of cytotoxic, growth regulatory and immunoregulatory functions. Whilst the pragmatic position "Does it matter how they work, if response is obtained?" holds in phase I/II studies, it will be difficult to unravel their physiological and therapeutic role in the setting of combination lymphokine and lymphokine/chemotherapy programs.
- What constitutes toxicity for an immunoregulatory agent? Should dose-response studies be designed solely around toxicites that do not reflect immunological response? Are the toxicity data required for chemotherapeutic agents appropriate for "biologicals"? These questions are particularly relevant for natural products whose maximum useful effect might be obtained at doses orders or magnitude lower than those producing toxic effects.

While all would agree that, within clinical studies in oncology, immunological responses may be modified in both a potentially advantageous and a potentially deleterious manner, the pressure to demonstrate antitumor effect may overshadow the no-less-important aspect of dissection of the normal physiological regulation of immune response and its perturbation by malignant disease. It behooves all involved in this area of research to apply the same rigorous standards of investigation to the clinical application of lymphokines in oncological practice as must be applied in the analysis of their physiological role in regulation of the immune response.

S.D. Sutcliffe, M.D.
Co-chairman of Conference

SUMMARY OF SESSION ON PARTICLES

Radiation therapy in Ontario is carried out using either photons or electrons. However, throughout the world, a variety of institutions are engaged in trials involving the use of particles such as neutrons, protons, heavy ions, and π-mesons. The purpose of this session was to consider the current situation with respect to particle therapy.

The first speaker, Dr. R.M. Henkelman, pointed out that, with respect to particle therapy, it was pertinent to consider these major phenoma: improved dose localization; increased biological effectiveness; and reduced dependence upon hypoxia. For neutrons, any major gain would only come from increased relative biological effectiveness (RBE) and a reduced oxygen dependence. These potential gains, in large measure, might be overcome by relatively poor dose distributions in many sites. For protons, the biological effects would be similar to those of photons but the dose distribution would be markedly improved. Heavy ions and π-mesons appeared to offer the advantage of improved dose distribution coupled with increased RBE and reduced oxygen dependence. Such machines, however, suffer from high initial and subsequent operating costs.

In addition to the phenomena discussed by Dr. Henkelman, Dr. J.D. Chapman suggested that reduced cell-cycle dependence and reduced repair also might affect therapeutic outcome. He pointed out that, in general, tumors that exhibit the greatest repair capacity, the greatest resistance to photon irradiation, or those with high fractions of hypoxic cells would be the best candidates for heavy particle therapy. Then he pointed out that in vitro assays, currently available or under development, might allow us to identify those tumors most likely to benefit from particle therapy.

Dr. Wm. Duncan opened his presentation on neutron therapy with a brief review of the biological factors which affect neutron therapy. He concluded that, because of reoxygenation, the presence of hypoxic cells was not the major rationale for considering neutron therapy. Rather, he believed that the critical factor was likely to be a reduced dependence of sensitivity on age in the cell cycle. He also cautioned that the RBE for late effects increases more rapidly at small photon doses per fraction than does that for early responding tumor; this can lead to unacceptable late complications unless adequate precautions were taken. After a brief review of available clinical data from neutron trials, Dr. Duncan concluded that neutron therapy must still be considered experimental. Future trials should employ large fractions over a short, overall time interval and should not make use of mixed photon and neutron schedules.

Dr. J. Munzenrider reviewed experience with proton beams at the Massachusetts General Hospital using the Howard cyclotron. The program, begun in 1973, has accrued over 1600 patients, predominantly patients with uveal melanoma, prostate

carcinoma, chordomas and chondrosarcomas, but also some soft tissue sarcomas, CNS tumors, and head and neck tumors. Based on this experience, Dr. Munzenrider concluded that protons must be seen as an evolutionary advance in radiotherapy and that the impressive clinical successes seen with uveal melanomas, chrodomas and chondrosarcomas warrant increased utilization and evaluation of protons and other charged particles.

G.F. Whitmore, Ph.D.
Chairperson of Session on Particles

EVALUATION OF FAST NEUTRON THERAPY*

W. DUNCAN, M.B., Ch.B.**
Toronto, Ontario

Radiological Principles

The first question posed was: What are the radiobiological principles supporting neutron therapy? In the 1960s, after Stone's initial studies, neutron therapy was re-evaluated because of the demonstration of the "oxygen effect", significant hypoxia in tumors, and the possibility that hypoxia may limit the radiocurability of some cancers. it is now thought that many cancers reoxygenate well during fractionated radiotherapy and hypoxia may not be so important as once thought. Provided there is reoxygenation between small-dose fractions, the "oxygen gain factor" of neutron therapy is small compared with x-rays unless there is a very large hypoxic fraction initially.

We must also consider the response of normal tissues which have to be included within the high-dose volume. Tissues such as the laryngeal cartilage, which contain a significant portion of hypoxic cells, are better treated by x-rays and neutrons should be used with caution.

Subsequently, it was discovered that the response of cells to neutrons is much less influenced by cell age than is the response to x-rays. At low-dose fractions, the relative biological effect (RBE) for S-phase cells compared with cells in mitosis is about 5. Following a dose of radiation, cells in the more sensitive phases are selectively killed leaving a relatively resistant population. Redistribution of the cells within the division cycle will bring more cells into the sensitive phases. The probability of that happening to an extent that may influence the clinical outcome will be much greater in rapid dividing tumors and tissues. Since the variation in radiosensitivity throughout the cell cycle is much less with neutrons, the redistribution of cells between fractions is less important than with x-rays. Neutron therapy may be particularly useful in slowly proliferating tumors, in which resensitization is much less than with rapidly dividing tumors. This potential advantage of neutrons has been called the "kinetic gain factor" and may prove to be more important than the oxygen effect. Of course, if after redistribution less than 50% of cells were in the resistant phase, then x-rays would be more effective than neutrons.

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*Abstract of a paper presented at the 11th Clinical Cancer Research Conference, held on September 28-30, 1987, at Geneva Park, Lake Couchiching, Ontario

**Radiation Oncologist, Ontario Cancer Institute, Toronto; and Professor of Radiology, University of Toronto

Three types of repair after radiation exposure have been demonstrated – recovery from sublethal damage, repair of potentially lethal damage, and slow repair. Quantitatively, the responses are very different after x-rays and neutrons. All cells show a diminished capacity to repair sublethal damage after neutron irradiation. The loss of the "shoulder" from cell survival curves explains the dependence of RBE of neutrons on the size of dose per fraction. The smaller the dose of x-rays, the greater the relative effect of neutrons. Over the dose range used in clinical practice, fraction size of neutrons does not influence the total dose required to achieve a given effect. However, with x-rays, a change in fraction size substantially affects the total dose required for similar end results. It has been found that the increase in total dose of x-rays required to achieve a given effect is greater as the fraction size is reduced for slowly dividing, late responding tissues than for rapidly dividing tissues. Most tumors, we believe, behave like rapidly dividing tissues and so may be much more effectively treated by small doses of x-rays.

Neutron iso-effect curves show little difference between early and late-responding tissues with dose over the clinical range. Consequently, the RBE for late normal tissue damage increases more rapidly for decreasing dose per fraction of x-rays than that for acutely responding tissues. Similarly, the RBE of neutrons for slowly proliterating tumors would be higher than for rapidly dividing tumors treated with small-dose fractions. By the same argument, rapidly dividing tumors would be better treated by accelerated fractionation of x-rays using small-dose fractions.

It is interesting that some tumors, considered to be relatively resistant to x-rays, have been shown to exhibit substantial repair of potentially lethal damage. Two tumors that show considerable repair of potentially lethal damage are malignant melanoma and soft-tissue sarcomas. This may explain, in part, the claims of enhanced response of those tumors to neutron irradiation after which no repair of PLD is demonstrated. Since the effect is dose dependent, enhanced response may be associated with fewer large-dose fractions.

Slow repair, which was first described in the lung but has been shown to occur in other tissues, is thought to be an intracellular recovery process observed in slowly dividing tissues after x-ray exposure. No slow repair has been demonstrated after neutrons. This may contribute to the greater effect of neutrons in slowly dividing normal tissues and tumors.

Practical and Technical Limitations

Much of the clinical work undertaken in the 1960s and 1970s was compromised by practical problems related to the equipment used. Most of the neutron beams were generated by cyclotrons which were often located at sites remote from the hospital-based radiotherapy facilities – sometimes 100 miles or more. Also, the cyclotrons often were made available for clinical work discontinuously and this

made recruitment of patients difficult. The beam energy was at times inappropriate, usually providing inadequate penetration. The beam alignment usually was fixed and horizontal which made patient positioning and field selection unsatisfactory and treatment planning less than ideal. Patients often were treated sitting, standing or lying on their sides. The deuterium/tritium generators have too low an output, which seriously limited their clinical application.

These practical difficulties quickly led radiation oncologists in the USA to explore the advantages of using a mixed schedule -- combining three fractions of photon irradiation with two fractions of neutrons each week. Equally important, these workers found that using neutrons alone was associated with unacceptably high levels of late normal tissue morbidity.

Clinical Trials Results

Most patients treated by neutrons have been recruited to Phase I/II studies. This review will concentrate on the results of randomized trials with some comment on recent encouraging results of Phase II studies.

The Atlantic sharply divided the scientific approach to the evaluation of neutron therapy. Almost all the initial trials in the U.S. used mixed schedules of neutrons and photons (Table I -- local control rates and rates of serious complications). The best indication of a real qualitative advantage to neutron therapy is an increase in local control with similar rates of morbidity in both treatment arms. The only significant benefit that has been demonstrated with mixed schedules is in locally advanced prostate cancer. Locoregional control and survival are both better in the group treated by neutrons and photons compared with photon irradiation alone. An apparent significant improvement also has been reported in local control in secondary neck nodes, but this may be accounted for by chance or by technical factors such as a higher dose to the nodes in patients treated with neutrons. No difference was observed in the control rates of the primary tumors or in the overall control rates of locoregional disease. Whether neck nodes are better treated by neutrons remains to be confirmed.

The lung cancer trial of Berlin-Buch is interesting because they reported a significant increase in local tumor control in the mixed schedule group. The end-point was histological assessment of the primary tumor at autopsy, which was performed in only 65% of patients. Survival was significantly better in patients treated with photons.

Often brain tumors, particularly the glioblastomas, are necrotic, thought to be hypoxic and respond poorly to photon irradiation. They seemed an obvious choice for the possible increased effectiveness of fast neutrons. None of the studies, using mixed schedules or neutrons only, have demonstrated any real advantage. It seems that the tolerance dose of neutrons for normal brain is lower than the 50% control dose for cerebral gliomas. Table II gives the results of Phase III trials of neutrons alone. The most encouraging results for neutron therapy have been reported from the MRC Cyclotron Unit in London. A highly significant

difference in local control rates were reported after neutron therapy of 74%, compared to only 19% after x-ray therapy. However, morbidity also was significantly increased in the neutron treated group. Many criticisms have been made of this trial -- its poor design, lack of a proper control group, non-uniform assessment, and of greatest concern was the very high radiation-related mortality in the neutron treated group; of 26 patients who were "locally well" at death, 8 (30%) died of treatment-related complications.

When clinical trials were started in Edinburgh, it was decided to use a neutron dose 5% lower than had been used at Hammersmith -- in the hope of reducing the unacceptably high level of radiation morbidity and mortality. The Edinburgh trial did not show any advantage for neutrons and the severe complications were greater in the neutron treated group. The Radiation Therapy Oncology Group trial of neutrons recruited very few patients, but the local control rate was significantly higher after neutrons than after photon therapy, which was associated with particularly poor results. It should be noted that in most of the trials, the serious complication rate is higher in the neutron treated groups. The relationship between local tumor control and the incidence of serious complications is well illustrated in the Amsterdam rectum/bladder trial in which two neutron doses were compared with a standard photon treatment.

The early report of the RTOG salivary gland trial have given rise to renewed enthusiasm for neutron therapy around the world. The trial includes only a small number of patients with tumors of several different histological types. There is a highly significant improvement in local tumor control in the neutron treated group (67%) compared with the photon treated group (17%). One problem with this result is the very poor control rate with photons, but more important is the significant difference in serious morbidity in the two groups. In the neutron treated group 8/13 patients had serious complications compared with 3/12 in the photon group. It has, therefore, not been established that the therapeutic ratio is increased using neutrons.

Two other types of tumor now are thought by some to be more effectively treated by neutrons. Several reports of treating inoperable or recurrent soft tissue sarcomas suggest that the local control rates may be better after neutrons than could be achieved by photon therapy. However, in almost all reports the good local control is associated with high levels of serious morbidity.

Dr. Schmidt of Essen, who has the greatest experience of managing these tumors with neutron irradiation, reworked a serious rare complication rate of 30%. He found the morbidity unacceptable and now recommends that neutrons be explored further as a small-field "boost" technique after wide-field photon therapy.

Dr. Catterall has reviewed the melanoma cases treated at the MRC Cyclotron Unit in London and suggests that this tumor, which responds unpredictably to low-LET radiation, responds much better to neutrons. These results need to be confirmed and compared in a controlled trial with what is thought to be optimal photon therapy.

Are Neutrons Useful in Clinical Practice?

Judgement on this questions has to be reserved. No good evidence supports the use of fast neutrons for epidermoid cancers. Their use to treat cerebral gliomas and CNS tumors may be disadvantageous. The trial of patients with prostate cancer needs to be repeated and the RTOG High LET Group plan to undertake the study. Some tumors such as salivary gland cancers, soft tissue sarcomas and malignant melanoma may be more responsive to neutrons. However, further clinical trials are required to ensure that the photon treatment is optimal by current standards and that the radiation doses are delivered, which ensure that the late normal tissue morbidity is similar. Neutron therapy remains experimental and does not yet have an established role in cancer therapy.

How May the Possible Advantages of Neutron be Further Exploited?

From the considerable experience of neutron therapy certain radiological principles seem clear. There is no scientific basis for using mixed schedules and the use of neutrons alone should be the subject of further clinical trials. Since fraction size is unimportant in the delivery of fractionated course of neutron therapy, large fractions should be employed. This should maximize the effect on tumors without any added detriment to late-responding, normal tissues. This technique also allows the overall treatment time to be kept short which may be advantageous in minimizing the effect of repopulation of tumors during prolonged fractionation.

Allowing time for redistribution of cells within the cycle to a more sensitive phase and for the reoxygenation is not so important with neutron therapy. Finally, as is clear from the reported clinical studies, much better selection of tumors for electric neutron therapy is required. Selection by simple histological classification is not adequate. More sophisticated techniques, using, for example, flow cytometry to assess the proportion of S-phase cells, other techniques of kinetic analysis, assessment of the content of tumors, cytochemical assays and measurement of oxygen content of tumors will have to be developed.

What Other Problems Have to be Resolved?

I would suggest our research should concentrate on three issues. They are equally important to photon and neutron therapy.

Firstly, we need to develop and validate objective criteria for the quantitative assessment of late, normal tissue morbidity. These are the crucial end-points when two different modalities or techniques of radiation therapy are to be compared.

Secondly, we need further insights into the cause and nature of the radioresistance of human tumors.

Finally, much effort is required to determine the importance of fraction size, total dose and overall treatment time in radiotherapeutics.

The answers, of course, may help us understand how low-LET radiations may be used to much better advantage if the regimens of fractionated treatment can be given a more rational basis than we have at present. Some cancer, I am sure, must be treated better by neutrons and their identification by techniques still to be established remains one of our greatest challenges.

TABLE I

Controlled Trials of Mixed Schedules

	PHOTONS			NEUTRONS		
	Patients	Local Control	Compli-cations	Patients	Local Control	Compli-cations
Head and Neck						
RTOG76/10	139	55%	5%	167	56%	6%
Lung						
Berlin-Buch*	100	20%	—	101	39%	—
RTOG79/07	38	61%	8%	36	53%	19%
Pancreas						
RTOG79/21	10	90%	10%	11	73%	20%
Cervix						
RTOG86/08	66	65%	11%	80	50%	19%
Prostate						
RTOG77/04*	36	31%	6%	55	77%	7%

*Difference is statistically significant

TABLE II

Controlled Trials of Neutrons Only

	PHOTONS			NEUTRONS		
	Patients	Local Control	Compli-cations	Patients	Local Control	Compli-cations
Head and Neck						
London	63	19%	4%	71	76%	21%
Edinburgh	80	45%	20%	85	45%	27%
EORTC	95	40%	25%	100	44%	22%
RTOG76/10*	12	17%	33%	23	52%	17%
Salivary Gland						
RTOG/MRC*	12	17%	25%	13	67%	62%
Lung						
RTOG79/07	38	61%	8%	30	57%	33%
Heidelberg	46	22%	22%	30	10%	30%
Pancreas						
RTOG79/21	12	8%	17%	13	38%	31%
Bladder						
Edinburgh	59	48%	12%	53	51%	55%
Manchester	59	–	8%	48	–	44%
Rectum						
Edinburgh	32	13%	6%	35	20%	17%
Amsterdam	31	–	3%	28	7%	7%
				26	38%	23%

*Differences are statistically significant at conventional levels

THE A, B, Cs AND R OF CHARGED-PARTICLE RADIOTHERAPY*

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Shortly after cyclotrons and other particles accelerators were developed, work began to apply such densely ionizing charged-particles in cancer treatment. Many years of cellular and animal research have defined potential advantages of charged-particles over photons for radiotherapy. Five of these potential advantages are: A) improved absorbed dose distributions; B) increased biological effectiveness; C1) less chemical modification, in particular, lesser importance of the radiobiological oxygen effect; C2) less cell cycle variation; and R) less repair of potentially lethal damage between dose fractions. I will discuss how each of these potential advantages might be exploited in charged-particle treatment protocols. A major disadvantage of charged-particle radiotherapy is high cost of the machinery to produce such particle beams.

New predictive assays have been developed to select tumors which might benefit most from charged-particle radiotherapy. In general, mammalian cells which are most resistant to photon irradiation display, have the largest relative biological effect with densely ionizing irradiation. Consequently, tumors whose cells exhibit inherent resistant radiosensitivities to photons might be most suited for radiotherapy with charged-particle beams. In addition, tumors known to contain large fractions of treatment-resistant hypoxic cells might also be candidates for charged-particle radiation. Laboratory assays have been developed to determine both inherent tumor-cell radiosensitivity and tumor hypoxic fraction.

It is likely that the major part of tumor radiotherapy will be performed with high-energy photon sources for the next few decades. Nevertheless, charged-particle radiothearpy facilities could play an important role in custom therapies of tumors which are inherently radioresistant to photons and/or contain large fractions of hypoxic cells.

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*Abstract of a paper presented at the 11th Clinical Cancer Research Conference, held on September 28-30, 1987, at Geneva Park, Lake Couchiching, Ontario

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CLINICAL RESULTS OF FRACTIONATED PROTON-BEAM RADIOTHERAPY*

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Since 1973, the Massachussetts General Hospital Radiation Medicine Service and the Retina Service of the Massachusetts Eye and Ear Infirmary have collaborated with the staff of the Harvard Cyclotron Laboratory most fruitfully in the study of fractionated, spread-out Bragg peak radiotherapy of human malignancies[1]. The project was initiated to assess tumor and normal tissue responses to fractionated proton-beam radiotherapy. Protons were known to have favorable physical characteristics, including a finite range in tissue as a function of their energy, and a sharply defined lateral beam edge. These properties gave potential promise for three-dimensional shaping of dose distribution in clinical radiotherapy. Since protons are low LET particles, they were not thought to have any significant biological advantage over conventional supervoltage x-rays. The specific goal of the project was to exploit the improved dose localization properties of the proton beam, to increase the dose delivered to the tumor while delivering the same or a smaller dose to adjacent dose-limiting normal tissues than those structures would have received with conventional fractionated x-ray techniques. Through September 16, 1987, 1619 patients had been treated. Major tumor categories included uveal melanoma (1125 pts), prostatic carcinoma (131 pts), chordoma and chondrosarcoma of the skull base and cervical spine (124 pts), soft tissue sarcoma (63 pts), CNS tumors (44 pts), and head and neck carcinoma (40 pts). This paper describes results in these patients, current treatment protocols, and future goals of the fractionated proton therapy project in Boston at the Harvard Cyclotron Laboratory.

Uveal Melanoma

Uveal melanoma patients have had proton therapy alone, with almost all patients receiving 70 Cobalt-Grey equivalents (CGE = proton Gy x 1.1) in 5 fractions over 7-10 days. Long-term results are confirming favorable initial impressions, which strongly suggested that proton treatment of uveal melanoma was an attractive conservative alternative to enucleation. Approximately 180-200 patients are being treated annually.

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Survival. In the first 128 patients treated, survival at five years was 80 ±5%[2]. Significant negative prognostic factors for survival include maximum tumor diameter, anterior tumor location and age over 59 years[3]. In 1006 patients treated through December 1986, Kaplan-Maier survival at 60 months was 78.5 ±3.6% for the entire group, and 97.5 ±3.5%, 85.8 ±4.2%, and 58.1 ±7.9% for patients with small, intermediate, and large melanomas, respectively (Fig. 1).

Tumor Regression and Local Control. Tumor regression was observed in all of the first 128 tumors treated, based on clinical, photographic, and ultrasonographic evaluation. Fourteen (12%) completely regressed, and 27 (21%) regressed to 1 mm or less in height[2]. Local control has been observed in more than 98% of patients, with additional treatment being necessary in 17 patients. Ten had enucleation, 5 were retreated with protons, and 2 were treated with photocoagulation.

Vision After Treatment. Useful vision, defined as visual acuity 20/200 (6/60) or better, was retained in 69 ±6% of the first 128 patients[2]. Visual prognosis after treatment is significantly associated with tumor height, distance of posterior tumor margin from the optic disc and/or fovea, pretreatment macular retinal detachment, initial visual acuity, and radiation dose to both disc and fovea, and to the lens[4]. The probability of having useful vision after treatment as a function of distance of posterior tumor edge from the fovea and optic disc is shown in Fig. 2 for 562 patients with pretreatment visual acuity 20/200 (6/60) or better. Useful vision was present at 24 months in 72% of 199 patients with tumor edge >3 mm from both structures, and in 53% of 363 patients with tumor edge <3 mm from either structure[5].

Eye Loss After Treatment. Enucleation was necessary in 5.7% of 1006 eyes treated through 1986, with eyes removed after treatment in 2 of 99 patients (2%) with small tumors, 20 of 566 (4%) with intermediate tumors, and 35 of 341 (10%) patients with large tumors. Rubeosis with neovascular glaucoma was responsible for 30 enucleations, with tumor growth, total retinal detachment with visual loss, and other causes necessitating enucleation in 10, 6, and 11 patients, respectively.

Summary and Future Studies. Clearly, the success of proton-beam therapy in treatment of uveal melanoma must be considered one of the major oncologic and ophthalmologic triumphs of the latter part of the twentieth century. Survival has not been compromised by this conservative treatment, compared to survival observed in enucleated patients[6]. Almost all tumors are being controlled and irradiated eyes conserved; over one-half of treated patients see as well or better than before treatment.

Future Studies. Protocols to evaluate different dose or fractionation schedules are being considered, in an effort to better preserve visual function after treatment in patients with either large tumors or tumors located within 3 mm of the optic disc and/or fovea. Efforts are also underway to develop a protocol to study adjuvant treatment with chemotherapy and/or immunotherapy in patients at high risk for the development of metastatic disease.

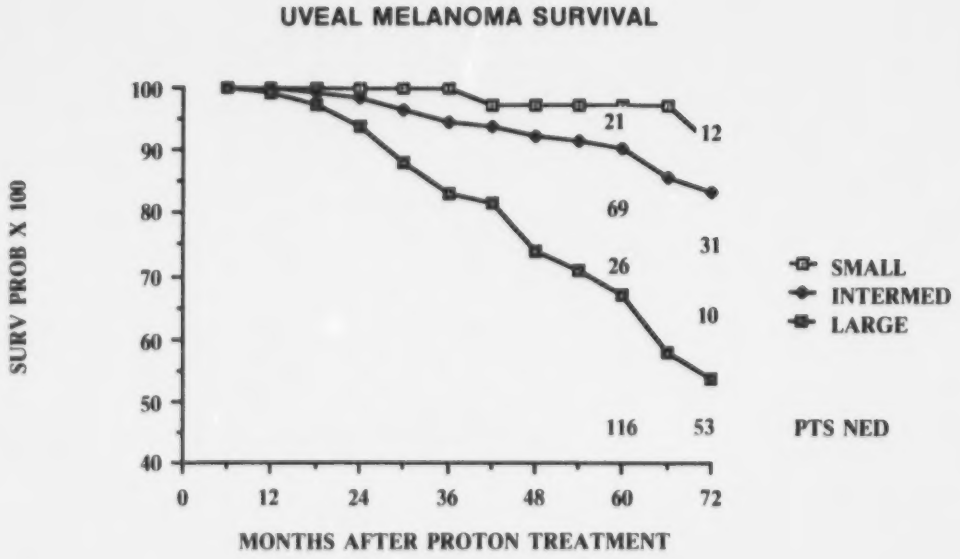

Fig. 1. Survival by Kaplan-Maier plot after proton treatment for patients with small (<3 mm high, <10 mm diameter), intermediate (3-8 mm high, 10-16 diameter), and large (>8 mm high, or >16 mm diameter) uveal melanomas. Numbers on curves represent patients surviving without disease at times shown; 116 and 53 patients are surviving NED (without evident disease) at 60 and 72 months, respectively.

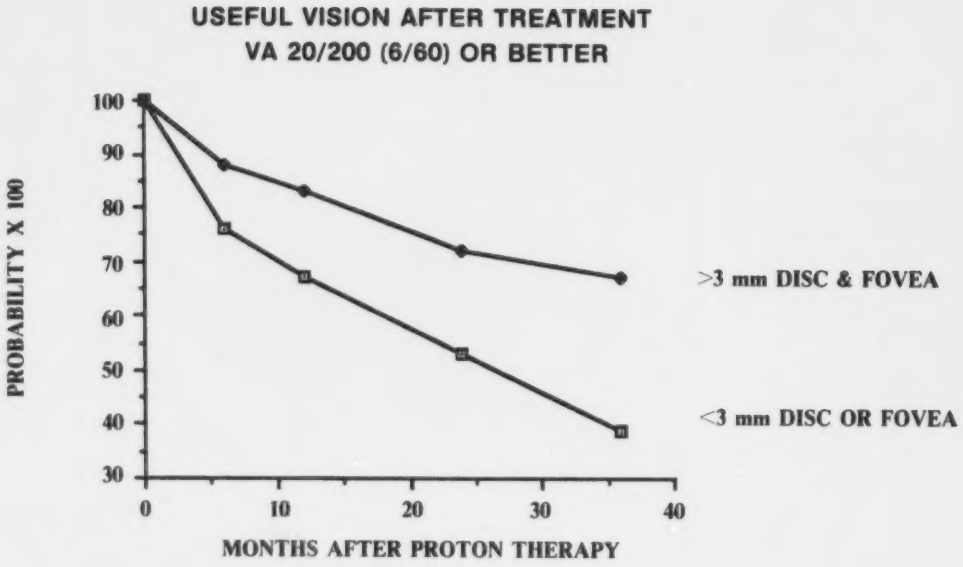

Fig. 2. Probability of having vision 20/200 (6/60) or better after proton treatment in 363 patients with posterior tumor edge <3 mm from optic disc or fovea and in 199 patients with posterior tumor edge >3 mm from both structures. All 562 patients had pre-treatemnt visual acuity of 20/200 (6/60) or better (plotted from data in Seddon et al[3]).

Chordoma and Chondrosarcoma

Patients with chordoma or chondrosarcoma of the skull base and cervical spine present a formidable management problem, since such tumors are usually not resectable, require a high radiation dose to achieve local control, and are adjacent to multiple dose-limiting normal structures, including the optic nerves and chiasm, temporal lobes of the brain, and the spinal cord and brain stem. One hundred and twenty-four such patients have received the majority of their treatment with the proton beam, with doses ranging up to 75 CGE; most have received 69-70 CGE at 1.8-2.1 CGE/fraction. Twenty-five to 30 such patients are treated annually. Treatment is labor-intensive and complex, with total planning time per patient being 30-40 hours, and each proton fraction requiring 40-70 minutes for set-up and treatment.

Local Control. In 68 patients with skull base tumors local control is 82%, with median follow-up of 34 months (range 17-152 months). There were seven in-field and one marginal recurrences. Historically, tumors in two-thirds of these patients would have been expected to recur following conventional photon treatment[7]. Tumors in 11 of 19 patients (58%) with cervical chordomas have not progressed, while tumors in 6 and in 2 patients in this category recurred within or immediately below the high dose volume, respectively.

Complications. The planning and treatment techniques, combined with the excellent dose-localization properties of the proton beam, have allowed us to keep doses to critical normal structures adjacent to these tumors below defined tolerance levels; relatively few significant complications have been observed. Three patients have had significant visual loss. Difficulty with memory and endocrine dysfunction have also developed in a few patients. Brain stem or spinal cord injury has not been seen in this patient group.

Survival and Clinical Trial. Disease-free survival approximates 75% in these patients, suggesting that we are achieving improved survival as well as local control. A randomized Phase III trial has been initiated through the Radiation Therapy Oncology Group, in collaboration with the Lawrence Berkeley Laboratory. The trial will evaluate prospectively tumor control and cognitive, endocrine, and visual function in patients with skull base chordomas and chondrosarcomas after doses of 66.6 or 72 CGE given predominantely with protons or with helium ions. Nine patients have been randomized through September 1987 at Massachusetts General Hospital, and 2 at Berkeley.

Meningiomas

Techniques employed in patients with chordomas and chondrosarcomas are also appropriate for treatment of discrete CNS tumors, such as meningiomas. No tumor progression has been observed in 11 meningioma patients (mean follow-up 31 months), including one with recurrent malignant meningioma, six with tumor

regrowth after and four immediately following subtotal resection of benign meningiomas. A protocol will be initiated, prescribing doses of 64-68 CGE for patients with malignant meningiomas, and either 50.4 or 59.4 CGE for patients with recurrent benign meningiomas.

Prostatic Carcinoma

In a pilot study, 66 patients with prostatic carcinoma received a perineal proton boost after photo therapy to the pelvis. Doses 15-20% above those conventionally employed were not associated with a greater risk of bladder and rectal complications[6]. In a Phase III trial, patients with $T^{2-3}N^{0-1}xM^{0}$ prostatic adenocarcinoma are being randomized to receive either an x-ray or a proton boost after photon pelvic treatment, to total doses of 67.2 Gy/36 treatments or 75.6 CGE/40 fractions, respectively. One hundred and thirty-five patients have been randomized through September 16, 1987. Patient accrual is expected to be completed in 1988.

Soft Tissue and Bone Sarcomas

Proton therapy has also been used as a boost after resection and photon treatment in patients with bone and soft tissue sarcomas, in order to limit dose to adjacent normal tissues, such as the eye, spinal cord, ovary, shoulder and hip joint. With a mean follow-up of 36 months, local control has been observed in 54/63 patients (86%). Fifteen patients with paravertebral sarcomas received a median dose of 66 CGE. Local control was achieved in 14 (93%), with median follow-up of 35 months. Spinal cord injury has not occurred.

Head and Neck Cancer

Proton-boost therapy has also been given to 40 patients with head and neck cancer. A submental portal has been employed in patients with floor of mouth and base of tongue tumors, while lateral and oblique portals are employed in patients with posterior pharynx and nasopharynx tumors. Local control was achieved in 12/19 (63%) patients with floor of mouth carcinomas. Future studies will involve boost therapy with protons or photons to floor of mouth and base of tongue patients, and continued pilot studies and comparative treatment planning efforts in patients with nasopharyngeal, parotid gland, and paranasal sinus carcinomas.

Other Sites

Two children with retinoblastoma have been treated with protons only. Special efforts are continuing to develop techniques and protocols for patients with

metastatic para-aortic lymph nodes from cervical carcinomas, and with superior sulcus (Pancoast) tumors of the lung, with five and two patients in each category having been treated, respectively. Comparative treatment planning studies have demonstrated the superiority of proton-dose distributions to photon-dose distributions in patients with bronchogenic carcinoma, para-aortic nodal metastases, nasopharyngeal carcinoma, and advanced thyroid carcinoma.

Current Indications for Fractionated Proton Therapy

Fractionated proton therapy is indicated for patients with uveal melanomas, who receive only protons. Patients with chordoma and chondrosarcoma of the skull base and cervical spine, meningiomas, and paravertebral sarcomas receive the majority of their treatment with the proton beam. A proton boost after photon therapy is given to patients with prostatic carcinoma, retroperitoneal and apical lung tumors, and cancers at selected head and neck sites.

The 160 MeV proton beam may have sufficient range (~16 cm in water) to treat primary mediastinal and pelvic tumors in some patients. Feasibility studies are planned for boost therapy in selected patients with lung, esophageal, bladder, rectal, and cervical cancers. Planning is actively proceeding for a new hospital-based proton medical facility at the Massachusetts General Hospital.

Protons are used for clinical radiotherapy in Villigen, Switzerland, at three sites in the USSR (Moscow, Leningrad, and Dubna), and at two Japanese centres (Chiba and Tsukuba). Helium ions, which are similar to protons in physical and biological properties, are used for clinical radiotherapy at Lawrence Berkeley Laboratory in California. Proton therapy may be re-initiated in the near future at Uppsala, Sweden, where fractionated proton therapy was first employed. Cyclotrons at Clatterbridge, near Liverpool, England, and in Orsay, France, may be modified for proton therapy of ocular malignancies. A new facility near Capetown, South Africa, will also begin proton-beam therapy within the relatively near future. A totally new clinically dedicated cyclotron is being designed and will be constructed at Fermi Laboratory near Chicago, Illinois, for ultimate installation at Loma Linda University in California. A new light ion medical particle accelerator will be constructed at Chiba, Japan. Other new particle therapy facilities are being considered at Berkeley, California (LIBRA), in Germany at GSI, near Darmstadt, at SIN in Villigen, Switzerland, and by a French-Belgian Consortium (EULIMA).

Summary

Protons are not "magic bullets"; proton-beam therapy is not a revolutionary development in the treatment of malignant disease. Rather, it must be considered as an evolutionary advance in radiotherapy practice, similar to improvements in dose distributions which were made possible when kilovoltage x-rays were supplanted

by supervoltage photons, and, more recently, by the availability of electron beam techniques.

However, the impressive clinical success achieved by the proton therapy program in Boston at the Harvard Cyclotron Laboratory, particularly in patients with uveal melanomas and with bony and cartilagenous tumors of the skull base and cervical spine, have served as powerful stimuli for a burgeoning interest in charged particle radiotherapy in the treatment of human malignancies.

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IMREG -- IMMUNOSUPPORTIVE STRATEGIES*

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My paper will outline our progress in developing biologics, which influence and/or modify human immune function. In particular, I will describe the isolation and properties of two endogenous immunomodulators from buffy-coat leukocytes. These biologics, designated IMREG-1 and IMREG-2, exert several important effects on cell-mediated immune function, including the ability to augment reactions of delayed hypersensitivity to recall antigens, such as tetanus toxoid. Such reactions are fundamental indicators of immune functional status, and frequently are lost in patients with AIDS, advanced malignancies and in aging.

A principal property of IMREG-1 is its ability to enhance the production of several biological response modifiers (lymphokines) by the CD4+ helper cells including interleukin-2 (IL-2), gamma-interferon and the migration-inhibitory lymphokines. IMREG-2 shares several properties with IMREG-1 and both IMREG-1 and IMREG-2 enhance the expression of receptors for IL-2, in response to antigen, on CD4+ cells.

In view of these several effects on CD4+ cells, an open Phase II trial of IMREG-1 has been carried out in patients with AIDS/ARC. The encouraging results have provided the basis for a randomized, double-blind, placebo control trial of IMREG-1 in patients with AIDS/ARC.

The chemical analysis of IMREG-1 indicates that the immunologically active molecules in this biologic are a tripeptide, Tyr-Gly-Gly, and a dipeptide Tyr-Gly. These molecules are chemically identical to the N-terminal amino acids of the enkephalins. The latter are potent opioid peptides and the molecular components of IMREG-1 may represent important links between the neuroendocrine and immune systems.

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UPDATE ON ALPHA INTERFERON*

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Lymphokines are molecules secreted by a variety of cells in response to stimulation by a number of different agents; they represent a communication network through which cells can interact in mediating antiviral, antiproliferative and immunomodulatory activity.

The interferons (IFNs), discovered in 1957 by Isaacs and Lindeman, were the first group of lymphokines to be identified and, as such, have been the most extensively studied and tested. Originally, natural alpha IFN was produced for clinical trials by the partial purification of the supernatant material after Sendai virus stimulation of the buffy coat from donated whole blood. This method was costly and labor-intensive; in addition, the product had a low-specific activity ($2x10^6$ u/mg of protein) and a purity of less than 1%.

The initial trials with this type of preparation were carried out in patients with osteosarcoma during and after primary resection. Strander and colleagues demonstrated a maximum tolerated dose (MTD) of $3x10^6$ u/day; the dose-limiting side effects were fever, fatigue, malaise and weight loss. When compared with historical controls, the IFN-treated patients showed some improvement, and studies in Scandinavia and in the U.S., using similar preparations, demonstrated antitumor effects in patients with indolent non-Hodgkin's lymphoma, multiple myeloma, renal-cell carcinoma and breast cancer.

In 1981, advances in recombinant DNA technology made available highly purified interferon preparations and clinical trials employing recombinant leukocyte interferon were begun in cancer patients. In the five years since its initial synthesis, alpha-2b interferon has passed through the initial phases of preclinical and clinical testing in over 2000 cancer patients representing over two dozen tumor types.

This review will summarize some of the Phase II and III trials in which alpha IFNs have shown promise, and will describe ongoing trials to further define the clinical utility of these agents. Table I sets out three categories of therapeutic efficacy for alpha IFN used in clinical trials in a variety of malignant diseases.

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Hairy Cell Leukemia

Quesada[1] showed that patients with hairy cell leukemia (HCL) has a dramatic clinical response to therapy with alpha interferon. A multicenter trial tested recombinant interferon (rIFN) alpha-2b (INTRON A, Schering Corporation, Kenilworth, N.J.) administered subcutaneously (SC) at $2x10^6$ u/m^2 given thrice weekly (TIW) in patients with progressive HCL. Of 216 evaluable patients, 169 had undergone splenectomy and 95 received chemotherapy. The marrow of 96% of the patients had >50% hairy cells. Complete response (CR) was defined as a normal complete blood count (CBC) and <5% hairy cells in the marrow. Partial response (PR) was signified by a normal CBC; minor response (MR) was determined by normalization of a subnormal hematocrit or granulocyte or platelet count. CR, PR, and MR were induced in 4%, 74%, and 11% of patients, respectively. Usually normalization of the CBC required two to five months of treatment

The objective responses in 89% of patients (CR + PR + MR) produced a marked reduction in or absence of life-threatening infections and independence from transfusions. The responsiveness of HCL in 47 patients, who had not undergone splenectomy, did not differ signigicantly from that in 169 splenectomized patients. After one year of therapy, responders were randomized to continue therapy for six months or to be observed. This well-tolerated outpatient regimen induced durable responses and dramatic improvement in the quality of life in almost all patients with progressive HCL.

Trials are underway to determine the optimal length of treatment of responding patients and the minimum amount of drug for treatment and maintenance phases.

Myeloma

Preclinical studies demonstrated the antiproliferative activity of natural and rIFNs against myeloma-cell lines. In a Phase II study of INTRON in resistant multiple myeloma[2], several regimens were tested including: (a) daily intravenous induction followed by subcutaneous maintenance; or (b) low-dose ($2x10^6$ u/m^2/d SC TIW) induction followed by maintenance therapy. Of 38 evaluable patients, 19 were refractory and 19 had relapsed at entry; 25/38 had received therapy earlier with multiple drugs. Responses were seen among 2/19 refractory patients and 5/19 relapsing patients. Three of seven responders had responses lasting over one year, and most patients on study had relief of bone pain. Currently, combinations of INTRON with chemotherapeutic agents are being studied as first-line therapy; a Phase I-II trial, comprising of 30 previously untreated patients treated with INTRON, melphalan and prednisone, showed a 75% overall response rate with a duration of 10+ months[3].

Renal-Cell Cancer

An initial trial, using leukocyte IFN, reported some temporary stabilization or objective responses in patients with metastatic renal-cell carcinoma. Other

investigators have corroborated this experience.

It appears that approximately 20% to 25% of patients have objective responses, and, although pulmonary metastases seem to be most responsive other sites of disease have shown improvement, including an intracranial metastasis[4]. In a 44-institution co-operative study recently reported from Japan[5], an overall response rate (CR + PR) was achieved in 17.7% of 226 evaluable patients. The median period to achieve CR or PR was 45 days (range – 22-211 days).

Studies adding vinblastine to INTRON therapy have not shown an improval in response rates to those seen with INTRON alone. Currently a trial is underway to study IFN therapy given in an adjuvant setting following resection of renal carcinoma at high risk of recurrence.

Chronic Myelogenous Leukemia

Several uncontrolled studies have suggested that alpha IFN is effective in the treatment of chronic myelogenous leukemia (CML). Hill et al in 1982, described three patients treated with high-dose non-rINF given intravenously. Two of them were in blast crisis at the time of treatment, and the authors concluded that such treatment was effective. Recently, Talpaz[6] described 17 patients with Philadelphia-chromosome-positive CML treated with rIFN alpha-2 at a dose of $5x10^6$ u/m^2/d. Fourteen responded to treatment, of whom 13 had a hematologic remission and one had a partial hematologic remission. In six of those with hematologic remission, there was complete suppression of Ph'-cells on at least one occasion. Niederle[7] administered INTRON to 21 patients with CML at an initial dose of $4x10^6$ u/m^2/d. Of 16 evaluable patients, including one in blast crisis, nine obtained hematological remission; at early follow-up, 4/8 patients showed a reduction in Ph'-positive metaphases by as much as 50%.

A Phase III trial is underway to compare the survival of patients treated with INTRON to those treated with conventional therapy (hydroxyurea); it is hoped to determine whether the improvement in cytogenetic status translates into survival advantage.

Kaposi's Sarcoma

Initial clinical trials of IFN in the treatment of AIDS-related Kaposi's sarcoma have been encouraging. Workers have reported response rates of up to 50%, using various doses, schedules, and routes of administration[8-10]. Real and colleagues[8] have noted that neither GI involvement nor large tumor burden significantly decreased the response rate; the best correlate of response was the absence of prior OI. Table III summarizes the results of three large studies using alpha rIFN in the treatment of AIDS-related Kaposi's sarcoma.

Of additional interest, recent studies suggest that alpha IFN may reduce the

viral shedding in the disease. Preliminary studies at the National Institute of Allergy and Infectious Diseases in Washington, D.C. have shown that 7/11 patients receiving INTRON have achieved transient negative viral cultures while receiving doses between 15-35 MIu daily or every two days. Krown and colleagues, using IFN alpha 2a, have described culture results in three groups of Kaposi's sarcoma patients (verbal communication at the 2nd International AIDA Conference, June 1986, in Paris, France).

Lymphomas

Several workers have shown that alpha IFN is active in non-Hodgkin's lymphomas: low-grade lymphomas are the most sensitive. Wagstaff[11] showed a 50% response rate among 34 evaluable patients with low-grade non-Hodgkin's lymphoma; among the 16 previously untreated patients, the response rate was 69%. Current areas of investigation include the co-administration of chemotherapy and INTRON. Rohatiner and colleagues[12] have concluded that combination therapy can be safely administered and that the response rate to chlorambucil and INTRON was higher than that with chlorambucil alone.

Ovarian Cancer

Epstein, in 1980, showed that ovarian cancer was sensitive to the anti-proliferative effect of human leukocyte IFN in vitro using the semi-solid agar technique. Since that time, Phase II studies have been done in patients with advanced measurable disease using various alpha IFN preparations, doses and routes of administration. The Gynecologic Oncology Group[13] reported 2/28 CR, 3/28 PR and 14/28 stable disease after the systemic administration of IFN.

Recently, Berek and colleagues[14] evaluated intraperitoneal INTRON as salvage immunotherapy in Stage III ovarian cancer. Of 22 surgically evaluable patients, four (36%) achieved a pathological complete response, one (9%) achieved a partial response, and six (55%) had progressive disease. Five of seven (71%) with residual tumor <5 mm had a surgically documented response.

A Phase III trial is underway to compare intraperitoenal INTRON at a dosage of 50 MIu weekly to intraperitoneal cis-platinum at a dosage of 90 mg/m^2 every two weeks in the setting of minimal residual disease following chemotherapy.

Bladder Cancer

Superficial, transitional bladder cancer is sensitive to intravesically administered INTRON. Recently at Stanford, Torti et al, administered escalating doses of INTRON (50-1000x10^6 units). Patients with high-grade intraepithelial neoplasia

had a 26% complete response rate. An additional 16% had complete resolution of their carcinoma in situ, however the subsequent appearance of a low-grade transitional cell carcinoma suggested that the IFN might have a maturational as well as a cytolytic effect on these tumors. Studies are underway to determine the optimal dose and length of treatment.

Conclusion

Alpha IFN is an important first member of a group of biologic response modifiers available for use in treating malignancies. Other indication not discussed in this review, i.e. the treatment of chronic hepatitis and prophylaxis of viral URIs, may have notable clinical significance as well. Numerous clinical trials, combining IFNs with chemotherapy, immunomodulators, and using new schemes and routes of administration are leading to a new understanding of biologic response modifiers and the biology of tumors.

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TABLE I

Activity of Alpha Interferon Against Various Malignancies in Phase II Studies

Active	Hairy cell leukemia
	Chronic myelogenous leukemia
	Non-Hodgkin's lymphoma
	Cutaneous T-cell lymphomas
	Kaposi's sarcoma
	Multiple myeloma
	Malignant melanoma
	Carcinoid tumors
	Bladder cancer (intravesical)
	Ovarian cancer (intraperitoneal)
Inactive	Breast cancer
	Colon cancer
	Non-small cell cancer
	Prostatic cancer
	Acute myelogenous leukemia
Further study required	Chronic lymphocytic leukemia
	Acute lymphocytic leukemia
	Hodgkin's disease
	Osteogenic sarcoma
	Astrocytoma
	Renal cell cancer
	Small cell lung cancer
	Endocrine pancreatic cancer

TABLE II

Renal Carcinoma: Responses to Interferon

Evaluate Patients	Responses	IFN	References
19	5PR 2MR	IFN	Quesada et al *Cancer Res* 1983; **43**:950
24	2PR 4MR 6SD	rIFN-A	Enzig et al *ASCO* 1984; **3**:209
24	1PR 1MR	r-IFN-Alpha 2	Kempf et al *ASCO* 1984; **3**:228
54	1CR 11PR 1MR	IFN-Alpha A	Neidhart et al *ASCO* 1984; **3**:232
21	2PR 3MR 10SD	IFN-Alpha	Vugrin et al *ASCO* 1984; **3**:599
18	4PR	IFN-Alpha	Strayer et al *ASCO* 1984; **3**:619
17	5SD	rIFN-Alpha 2	Muss et al *AACR* 1984; **35**:231
30	9SD 5MR 1PR	rIFN-Alpha A	Schnall et al *ASCO* 1986; **5**:890
TOTAL 190	26PR 16MR 32SD		

TABLE III

Summary of Results in Kaposi's Sarcoma

Dose, Route, Type of IFN	Duration	Number of Evaluable Patients	Overall Response Rate	Reference
36-54 x 10^6 u/d IM IFN alpha 2	4 weeks	34	38%	8
3 x 10^6 ud IM IFN alpha 2a	4-8 weeks	36	3%	8
30 x 10^6 ud IM escalated over 10 days IFN alpha 2a	8 weeks	27	15%	8
1 x 10^6 u/m^2/d IM on alternate weeks IFN alpha 2b	8 weeks	10	20%	9
50 x 10^6 u/m^2/d IV alternate weeks IFN alpha 2b	8 weeks	19	32%	9
30 x 10^6 u/m^2/d SC IFN alpha 2b	8 weeks	61	31%	9
7.5 x 10^6 u/m^2/d IM IFN alpha-N1	21 days	9	22%	10
15 x 10^6 u/m^2/d IM IFN alpha-N1	20-30 days	10	9%	10
25 x 10^6 u/m^2/d IM IFN alpha-N1	28 days	8	59%	10

TUMOR NECROSIS FACTOR*

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Tumor necrosis factor (TNF) was first described by Carswell and Old in 1975 as a factor in serum from endotoxin-treated mice which had been sensitized with BCG. Serum from these mice cause hemorrhagic necrosis, and in some cases complete regression of certain transplanted murine tumors[1].

Historical descriptions of what now is called TNF can be found in the scientific literature in the latter part of the nineteenth century, and largely are attributed to observations by William Coley, although some suggest that the notion of bacterial infection causing tumor regression was part of a widespread lore of the time[2-4].

Initial studies of the in vitro and in vivo activity of TNF, and early patient studies, were hampered by a shortage of TNF and contamination of existing supplies with other cytotoxins. However, since the successful cloning of the human genes responsible for TNF production, and subsequent large-scale recombinant TNF (rTNF) production in 1984[5], a great deal of detailed information concerning the biologic and antitumor effects of TNF has become available, and many Phase I clinical trials are now underway.

TNF (TNF-alpha) one of many polypeptides, which act as cytotoxins, is derived from activated macrophages; it is identical with "cachectin", a molecule first described by workers interested in the mechanism of cachexia in certain infectious and malignant diseases[6-8]. It must be distinguished from lymphotoxin (TNF-beta), a product of activated lymphocytes, which shares about approximately 30% homology with the TNF molecule[9]. Lymphotoxin also shares many of the biologic properties of TNF in experimental systems.

Human TNF, in its mature form, consists of 157 amino acids and has a molecular weight of 17,000. The molecule is derived from a precursor which is 233 amino acids in length.

Biological Activity of TNF

Inducers. TNF production is induced by several substances, such as endotoxin (bacterical lipopolysaccaride), which causes TNF secretion from macrophages. Concanavalin A is also able to induce TNF production from some T-cell clones.

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It is possible other TNF inducers will be identified; the fact that patients with parasitic infections have measurable TNF levels indicates that more inducers exist than those mentioned. It is of specific interest that measurable serum levels of TNF have not been noted in patients with cancer or cachexia due to malignant diseases or other causes.

Cytotoxicity. In experimental systems, TNF exhibits both cytotoxic and cytostatic activity in vivo and in vitro in some, but not all tumor lines. It is not cytotoxic to normal cells[10-13]. The mechanism by which TNF exerts its antitumor effect is not known, though several facts are now apparent. The presence of TNF receptors on malignant cells seems to be a necessary, but not a sufficient, condition for cell kill. The synergy between TNF and interferon-gamma (IFN-gamma) in some experimental systems[14,15] is due, in part, to the induction of TNF receptors by IFN-gamma, but this does not explain entirely the synergistic observation. The cause of TNF-induced cell death is the subject of considerable speculation. Fragmentation of target cellDNA has been observed in L929 cells when exposed to TNF. In addition, TNF alters the metabolism of polyunsaturated fatty acids and causes enhanced synthesis of prostaglandins which may promote the generation of cytotoxic free radicals. Other contributory metabolic changes include mobilization of glycogen to the energy pool and production of lactate with resultant fall in pH. Finally, it has been proposed that TNF might activate target cell lysosomal enzymes and release proteases. In short, there is no consensus concerning the general mechanism of TNF cell killing, but it is clear that TNF alters cellular metabolism and enzyme function in a multitude of ways, many of which might result in cell death. Clearly all of these mechanisms are directed towards explaining in vitro cell killing induced by TNF. In vivo, other indirect and immune mechanisms may also play a role[16].

Other TNF effects. As noted above, TNF has biologic effects other than cytotoxicity. In other experimental systems, it decreases lipoprotein lipase with resultant lipemia[17]. It induces vascular endothelial changes, and also promotes the release of interleukin-1 by monocytes and endothelium[18,19]. This, in turn, increases the expression of an endothelial polymorphonuclear-leukocyte-adhesion molecule. These effects indicate that TNF and other cytotoxins play a role in the process of inflammation. Indeed, TNF injected intradermally results in a reaction that resembles a delayed skin test.

Physiologic role of TNF. The physiologic role played by TNF is uncertain. As argued above, this molecule probably is involved in producing some of the changes accompanying the inflammatory response. How it interacts with other mediators and its role as an antitumor molecule in the natural setting is uncertain. There is no evidence to date that malignant disease induces measurable TNF release; this does not mean, however, that its observed cytotoxic activity cannot be exploited in cancer therapy.

Strategies of Clinical Development of TNF in Cancer Therapy

Several variables can be considered when designing strategies of clinical development of biologics:

(a) DOSE: optimal immunomodulatory dose, which might best be tested in an adjuvant setting, vs maximum tolerated dose (MTD), in which the drug is treated as a "cytotoxic" and tested in advanced or adjuvant disease settings;

(b) ROUTE: intravenous, intramuscular and subcutaneous routes are all possible;

(c) SCHEDULE: schedules of administration may be continuous (e.g. by daily subcutanous injection), pulse (e.g. daily x 5 days every 3 weeks), or intermittent (e.g. Monday, Wednesday, Friday).

The rationale for specific strategies depends upon knowledge of mechanism of action and other preclinical data. Unfortunately, because we have so little information regarding the mechanisms of TNF's cytotoxicity, strategies to date have been empirical. In addition, consideration has been given to using schedules of TNF administration which will simplify its eventual combination with chemotherapeutic agents and other biologics such as interferon. Initial strategies of Phase I development of recombinant TNF (rTNF) by the National Cancer Institute (which has a co-operative developmental program with Genetech, Inc.) include the use of TNF in MTD, in intravenous and intramuscular routes and in continuous, pulse and intermittent schedules. Of these, only intravenous rTNF given in pulse and intermittent schedules will be studied in Phase II single-agent trials.

Table I shows toxicities seen in Phase I trials to date. Hypotension in the intravenous "bolus" administration of rTNF, local skin reactions in the intramuscular schedule, and neurotoxicity in the continuous infusion schedule are the dose limiting toxicities. Fever, chills and headache are nearly universal but weight loss, disseminated intravascular coagulation, and shock have not been seen[20,21]. Rare antitumor responses have been documented in Phase I, but only at the conclusion of Phase II studies can we make an assessment of the single-agent antitumor activity of rTNF.

Future developmental strategies will build on the Phase II single-agent results. However, because of preclinical observations of synergistic antitumor effects, plans are underway to study rTNF in combination with interferon-gamma and cytotoxic chemotherapeutic agents in Phase I trials.

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TABLE I

TNF Toxicity in Phase I Trials

Frequent/Universal:	Fever
	Chills
	Headache
	*Hypotension
	(at highest doses IV)
	*Local reactions (SC,IM)
	Fatigue
Occasional:	Nausea
	Myalgia
	Transient ↑ liver enzymes
	Mild ↑ triglycerides
	*Neurotoxicity (CI only)

*Dose limiting toxicity in certain schedules

MONOCLONAL ANTIBODIES: DIAGNOSTIC AND THERAPEUTIC APPLICATIONS*

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Since the development of hybridoma technology by Kohler and Milstein in 1974, many workers have applied monoclonal antibodies to various non-hematologic malignancies. Currently, the four categories of applications under study are immunoassays, immunohistology, in vivo radioimmunolocalization, and immunotherapy.

At present, the following immunoassays are available commercially – carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (beta-hCG), CA19-9, CA125, CA15-3 and the estrogen and progesterone receptor assays. Since the original polyclonal immunoassay, available monoclonal antibody CEA immunoassays have been improved technically with respect to sensitivity, rapidity and ease of performance but have not improved greatly in specificity. We may make further progress in obtaining monoclonal antibodies that are specific for CEA because the genes for CEA and NCA have been cloned. There are no major differences in the sequences of CEA and NCA except that there are fewer repeats in NCA gene (6 vs 1 to 3 repeats). It appears that the CEA gene is post-translationally controlled because, as the Stanners and Fuks group have demonstrated, mRNA of CEA is present in both carcinoma of the colon and in normal colon, while the CEA protein is detected only in carcinoma of the colon. We need to examine the sites of carbohydrate attachment for differences among the various carcinomas if we are to determine if monoclonal antibody specificity is possible.

CA19-9 is a glycolipid which is detected in pancreatic and gastric carcinoma, as well as in pancreatitis and on normal gastric and gallbladder epithelia. In patients with pancreatic carcinoma, it is more sensitive than CEA, though it is not more specific. At present the CA19-9 immunoassay is most useful for monitoring the clinical course of pancreatic carcinoma.

CA125 is a glycoprotein which is present on the coelomic epithelium during embryonic development. The CA125 immunoassay appears to be superior to the CEA immunoassay for monitoring the clinical courses of ovarian carcinoma. In those who have an elevated CA125 level, it has been suggested that the slopes and

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plateaus of serial CA125 serum level are more important than whether the serum CA125 level is within the normal limit. This immunoassay should permit earlier assessment of the response to therapeutic interventions. While a normal serum CA125 level does not correlate with the absence of disease, it has been shown that patients with an elevated CA125 level do not have a prolonged disease-free interval. Finally, a preliminary study has demonstrated that the immunoassay for CA125 can be used as a screening tool for ovarian carcinoma. Completion of a clinical trial in the U.K. on 30,000 postmenopausal women should tell us more.

CA15-3 is an antigen found in breast carcinoma. Its serum immunoassay is not very senstitive and, at present, its clinical usefulness is limited to patients who have detectable levels.

The estrogen and progesterone receptor (ER and PgR) immunoassay (EIA) and the immunocytochemical assays (ICA) have been extensively evaluated in Europe and the U.S. The ER-EIA and PgR-EIA are solid-phase "sandwich" assays, which can detect 0.2 fmol R/mg cytosol protein. Correlation with the conventional dextran-coated-charcoal, steroid-binding assay (DCC-SBA) is greater than 90% despite the fact that the DCC-SBA measures only the unbound receptor, while the EIA measures both the bound and unbound receptor. The ICA qualitatively assesses the receptor content in breast carcinoma and hence can be used to determine if there is a population of carcinoma cells, which lack receptors, while the EIA is positive. The EIA and the ICA can be applied to smaller tissue samples including needle aspirates, and used in clinical situations where a biopsy specimen is not available for evaluation.

In conclusion, most of the current immunoassays are useful for monitoring the clinical course of disease. Further immunoassays may become available if we isolate monoclonal antibodies, which either recognize peptide sequences or carbohydrate chains, provided that the monoclonal antibodies have sufficiently high affinities to render the immunoassays sensitive enough to detect small tumor burdens. Carbohydrate chains may be an important source of antigens for evaluation because the carbohydrate chains are added after protein synthesis by the gene-encoded anzyme glycosyltransferase. Evidence exists for altered carbohydrate expression in tumors because the blood-group antigens, which are absent in adult colon, are detected in the fetal gut and adenocarcinoma of the colon.

Also monoclonal antibodies are being evaluated for their application in vivo radioimmunolocalization studies for the presence of tumor and their metastatic deposits. Detecting monoclonal antibody uptake is limited by the system used for detection, namely, persistent blood-pool images, non-specific uptake of the monoclonal antibody and the choice of radioisotope used to label the antibodies. Studies are in progress to reduce these limitations. Detection has been improved using emission-computed tomography instead of the traditional gamma counter cameras. Blood pool images have been reduced by delaying the onset of scanning for 24 to 72 hours after injection. Non-specific uptake has been reduced by

monoclonal antibodies which have minimal cross-reactivity with normal tissues and antibody fragments. A murine study by Beatty concluded that non-specific uptake may be reduced further by pretreatment with unlabelled antibody before the immunolocalization study. Furthermore, one needs novel approaches to determine the role of monoclonal antibodies in detecting the presence of disease; these include their use in lymphangiograms, and the use of a hand-held probe during operations to detect metastatic disease in the lymph nodes.

Radioimmunolocalization studies are also important forerunners for immunotherapy because they permit one to assess the degree of uptake of the monoclonal antibodies by deposits. As well, these studies permit us to assess the effects of in vivo administration of xenogenic proteins. Such evaluation is particularly important because most of the available monoclonal antibodies are of murine origin and elicit a human antimouse antibody response (HAMA). Current Phase I-II trials are determining dosages as well as the significance of the HAMA response in immunotherapy.

It has been proposed that monoclonal antibodies behave like magic bullets in immunotherapy. Conjugated to drugs, radioisotopes or toxins, they would deliver the conjugate directly to the tumor without the former becoming bound to non-tumor cells. Studies now in progress will determine which of the conjugates is preferable.

Drug antibody conjugates may be difficult because, to be effective, the drug must enter the cell and be liberated. Drug delivery also may be limited by the number of drug molecules which may be conjugated to each monoclonal antibody.

B-emiters have the advantage, not only that they exert their effect without crossing the cell membrane, but also can kill more than one cell. This is extremely important in tumors with a poor vascular supply where the monoclonal antibody may not have access to all of the cells.

Toxins have the advantage that only one molecule is required to kill the cell, thus avoiding the need to link a large number of molecules to the antibody. Furthermore, it does not require a high antigen density to ensure the delivery of sufficient antibody conjugate to the cell to achieve a therapeutic dose.

The use of multiple monoclonal antibodies directed to known epitopes could increase their effectiveness by increasing the amount of antibody bound to the cell (if each of the monoclonal antibodies recognizes a different epitope).

Finally, we require further innovations in monoclonal antibody production technology and enhancement of the methods of delivery. Currently under investigation are the use of quadromas, adjuvant therapy with biological response modifiers, monoclonal antibody with verapamil, and the use of radiation before monoclonal antibody administration.

In conclusion, monoclonal antibodies are available for serum immunoassays to monitor the clinical course of some of the non-hematologic malignancies. Further use of immunoassays for screening, such as the CA125 for ovarian carcinoma, is under investigation. Other monoclonal antibodies may become

available as we learn more about alterations of cell-surface molecules in malignant states. Also under study are the use of monoclonal antibodies for in vivo radioimmunolocalization studies and for immunotherapy. However, we need more information about the dosage of monoclonal antibodies to be used, what the monoclonal antibodies should be conjugated to, and how they are to be administered before we can draw accurate conclusions about their clinical usefulness.

References are available upon request from:

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IMMUNOCONJUGATES IN THE TREATMENT OF CANCER*

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The concept of using antibodies to target antineoplastic therapy can be traced back to Paul Ehrlich who, in 1906, proposed using "bodies which possess a particular affinity for a certain organ ... as a carrier by which to bring therapeutically active groups to the organ in question". With the subsequent development of hybridoma technology by Koehler and Milstein in 1975, interest in this approach has been renewed.

A variety of agents, which have been linked chemically to monoclonal antibodies to allow to be targeted to tumor-associated antigens, include radionuclides, toxins, drugs, antibodies and biological response modifiers.

In selecting an antibody for conjugation, one must consider:

i) the affinity of the antibody with its target antigen, both before and after conjugation;
ii) the dose of antibody to be used;
iii) the route it will be administered;
iv) how it is cleared and metabolized; and
v) the possible development of a human antimouse antibody response.

Important factors to be considered when constructing an immunoconjugate include:

i) the activity and stability of the conjugate;
ii) its overall molecular weight;
iii) the properties of the antigen to be targeted (modulating or non-modulating); and
iv) effects of the conjugate on bystander cells which do not express the target antigen.

Tumor parameters requiring consideration include:

i) the size of the tumor mass;
ii) the proportion of cells expressing the target antigen in the tumor mass;
iii) the target antigen density on the tumor cell surface;
iv) the fate of the antigen-antibody complex (e.g. shed, internalized);
v) the degree of vascularization of the tumor;
vi) the degree of necrosis present; and
vii) the presence of circulating antigen.

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*Abstract of a paper presented at the 11th Clinical Cancer Research Conference, held on September 28-30, 1987, at Geneva Park, Lake Couchiching,Ontario

**Clinical Associate, OCTRF Hamilton Regional Cancer Centre; and Terry Fox Fellow, Department of Pathology, McMaster University, Hamilton

Radioimmunoconjugates have been developed for both imaging and therapy. Isotopes with short range and high energy emissions appear to be best for therapy. These conjugates are able to overcome antigenic heterogeneity and do not require internalization to achieve their effect. However, on systemic administration only a very small fraction of the conjugate reaches the target, usually in the range of 0.01% of the injected dose per gram of tumor.

Clinical trials with radioimmunoconjugates have included:

i) T101/I-131 conjugates in the treatment of cutaneous T-cell lymphoma with 2/6 patients having short-lived partial response (2 months);

ii) Lym-1/I-131 conjugates in non-Hodgkin's lymphoma – here 6/10 patients had greater than 60% reduction in measurable disease; and

iii) anti-ovarian monoclonal antibody/I-131 conjugates given intraperitoneally to patients with advanced ovarian carcinoma; 4/12 patients achieved a complete response for 3-24 months after treatment.

A variety of toxins have been conjugated to antibodies and most of these studies have been carried out using the ricin-A chain toxin. These conjugates require internalization to exert their effects on ribosomal protein synthesis. As well, they would not be expected to kill antigen negative variants. The in vivo use of these conjugates have been associated with a number of problems:

i) disruption of the conjugate by enzymes present in plasma;

ii) rapid uptake of conjugates by the liver; and

iii) the presence of free antibody competing with conjugate for target antigens.

The Xoma Corporation has carried out several clinical trials using ricin immunotoxins. In patients with metastatic melanoma, a Phase I trial, using an antimelanoma antibody/ricin A chain conjugate, produced one complete response in 22 patients treated. A subsequent Phase II trial, using the same immunotoxin, resulted in 3 partial responses in 36 patients. A Phase I trial in patients with metastatic colorectal cancer, using an anticolorectal cancer antibody/ricin A chain conjugate, had no responses in the first 11 patients treated.

A number of drugs have been coupled to antibodies. This approach has several theoretical disadvantages:

i) chemotherapeutic drugs generally are stoichiometric in their antitumor activity and thus large amounts of drug must be delivered to the tumor;

ii) there are significant losses in immunoreactivity when more than 10 molecules of drug are linked directly to an antibody; and

iii) these conjugates would not be expected to have any effect on antigen-negative variants.

To date, clinical trials have been done with methotrexate and Adriamycin conjugates. Although toxicity was minimal or absent, no antitumor effects were noted.

The role of immunoconjugates in the treatment of malignancy remains to be defined. While awaiting potential solutions to the problems which have been identified, we need to concentrate on laboratory and clinical models which can achieve localization of large enough amounts of conjugate at the target site.

BIOLOGIC RESPONSE MODIFIERS: FUTURE DIRECTIONS*

OCTRF Research Lecture

S. SAKS, M.D.**, *San Francisco, California*

The current era of the biological therapy of cancer began some 75 years ago with the work of Coley, who observed that tumor regressions sometimes were temporally related to the occurrence of serious infections. He attempted to study the substances responsible for such antitumor effects. Through recombinant technology, we have access to pure preparations of the molecules, which potentially were involved in Coley's early observations. The study of such preparations suggests that the future direction of biological response modifiers (BRMs) may be to combine these agents and use them with other modalities of cancer therapy.

In the 1960s and 1970s, oncologists treating patients with biologics used preparations of micro-organisms such as BCG and C.parvum. The hope was that these would produce an immune response that would have secondary antitumor effects. Later, natural preparations of effector molecules such as interferon were produced and tested. Only small amounts of these materials were available for clinical testing and they were very expensive to produce. Also, many workers were concerned that other biologically active agents present in small amounts in these preparations might influence the results of both preclinical and clinical testing.

After the development of recombinant technology, large amounts of highly purified preparations of biologically active proteins became available for clinical testing. However, it was not until the 1980s that clinical trials with recombinant BRMs (rBRMs) began, greatly expanding our knowledge of these agents and the immune system, which they regulate. By studying recombinant products in the clinic, one could be sure that the results obtained were due to the specific protein being tested and not to minor biologically active components. The challenge now faced by those studying BRMs in the clinic will be to achieve meaningful clinical endpoints such as improved survival and quality of life as opposed to transient reductions in tumor mass. This presentation will focus on the clinical development of recombinant lymphokines – one class of BRMs – to illustrate some of the issues facing the development of the biological therapy of cancer.

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*Abstract of a paper presented at the 11th Clinical Cancer Research Conference, held on September 28-30, 1987, at Geneva Park, Lake Couchiching, Ontario

**Clinical Research Physician, Genetech, Inc., San Francisco, California; and Assistant Professor of Medicine, University of California, San Francisco

BRMs may function both by direct effects on tumor cells and by indirect effects mediated through immune system. The direct effects are similar to those seen with traditional cytotoxic chemotherapy, with agents used at their maximally tolerated doses (MTD). The indirect effects depend on immune effector mechanisms, which are incompletely understood at this time. For the most part, early studies with BRMs emphasized an evaluation of their indirect effects. Interferon-alpha (IFN-alpha) was the first rBRM developed as an antineoplastic agent. Initial Phase I trials defined MTD and identified dose-limiting toxicities including constitutional symptoms, leukopenia and hepatic transaminase elevations. The Phase II studies were initiated in patients with selected malignancies most often at the MTD[1]. After it was shown that recombinant interferon-alpha (rIFN-alpha) was effective in hairy cell leukemia, it soon became apparent that doses well below the MTD could improve the quality of life, by decreasing the incidence of infection and transfusion requirements. IFN-alpha also is active in other diseases where dose intensity may be important, such as CML, melanoma, renal cancer and AIDS-related Kaposi's sarcoma. Immunomodulatory activity has been observed on natural killer and other lymphocyte cell populations, although the clinical relevance of these changes is not clear.

Interferon-gamma (INF-gamma) shares antiproliferative and antiviral effects with INF-alpha, but has unique immunomodulatory effects including macrophage activation and regulation of Class-II histocompatibility antigen. These immunologic effects may be important in both anticancer and anti-infective clinical applications. Early Phase I and II trials of INF-gamma have demonstrated clinical effects similar to INF-alpha, though with different spectrum of antitumor activity[2]. Recently, recombinant interferon-gamma (rINF-gamm) has been extensively studied as a BRM. Studies conducted at the National Cancer Institute in Frederick, Maryland, under Drs. Steis and Urba, have documented the indirect immunomodulatory effects of rINF-gamma[3]. After complete resection of all known disease (deep Stage I or Stage II disease), patients with high-risk melanoma received varying doses, routes and schedules of INF-gamma. The immunologic endpoints chosen for evaluation included monocyte-macrophage activation as measured by peroxide generation, and induction of Fc receptor and HLA-DR antigen on peripheral blood mononuclear cells as indirect measures of antibody-dependent cellular cytotoxicity and regulation of cytotoxic lymphocyte function, respectively. Maximal stimulation of all parameters was seen at a dose of 100 mcg/m^2, administered by daily subcutaneous administration – a dose significantly below the MTD for this recombinant lymphokine. This regimen is well tolerated and suitable for long-term outpatient therapy. Now the NCI-sponsored co-operative group studies will evaluate the clinical value of this approach in the adjuvant setting in malignant melanoma and other malignancies. Prospective randomized clinical trials are necessary before the clinical benefit of inducing these immunomodulatory effects with rIFN-gamma can be determined.

When recombinant interleukin-2 (rIL-2) began clinical evaluation, the initial

focus was on its direct effects at the MTD. In this early testing, the antitumor effects were minimal although some responses were seen in patients with melanoma, renal cancer, and lymphoma. Emphasis then shifted to an evaluation of the indirect effects of IL-2 by way of LAK cell generation[4], presuming that regimens, which generated high levels and more sustained LAK cell activity, would have greater effects. The antitumor activity seen in renal cancer and melanoma appears to be significantly greater than that seen in earlier trials with IL-2 alone, although definite conclusions must await the results of ongoing randomized trials. The toxicity of IL-2 plus LAK cell therapy has been a major concern but perhaps, by using LAK cell activity as an endpoint, we will be able to predict which regimens and combinations will produce higher response rates with less toxicity.

Another lymphokine now in clinical trials is human recombinant tumor necrosis factor alpha (rTNF-alpha), which may also have antitumor activity both by direct cytotoxic and indirect immune effects. Preclinical studies have shown that TNF-alpha has both direct cytostatic effects against tumor cells[5] and that it is the principal macrophage product mediating antitumor cytotoxicity. Also, TNF-alpha is part of a complex "polypeptide mediator network" described by Lloyd Old[6] which influences the production and action of multiple cytokines. Phase I trials of rTNF-alpha have demonstrated that it can be given in a biologically active dosage range, which is associated with anticancer effect, without severe toxicity including shock and cachexia[7]. Phase II studies are under way to determine antitumor activity in specific tumor types, and to characterize further rTNF-alpha's indirect effects on the immune system.

Early clinical trials of the recombinant lymphokines indicate that an important future direction for BRMs is their use in combination therapy. This includes combinations of BRMs with each other as well as with cytotoxic chemotherapy, radiation, or surgery. Combination therapy with BRMs also may depend on their direct or indirect host-mediated effects. In contrast, combinations of cytotoxic drugs depend only on direct effects and rely on non-overlapping toxicities or attempts to reduce resistant tumor-cell populations. There may also be synergy in their mechanism of action; for example, that which has been postulated for the combination of 5-fluoruracil and folinic acid.

Usually, combinations of BRM therapy, based on direct effects, depend on synergistic interactions because toxicities tend to overlap and furthermore we know little about tumor-cell resistance to biologics. With respect to indirect effects, BRMs are used in combination because these agents are part of a complex immunoregulatory network and because they interact extensively under physiologic circumstances. Such combinations of BRMs now undergoing clinical evaluation include, for example, INF-gamma plus IL-2 and INF-gamma plus TNF. Patients who have responded to IL-2 plus LAK cell therapy appear to have, on their tumors, increased HLA-DR antigen, a factor whose expression is regulated by INF-gamma. Moreover, patients undergoing intraperitoneal therapy with LAK cells have high levels of INF-gamma in the peritoneal fluid[8]. These observations

suggest that the combination of IL-2 and INF-gamma might be therapeutically useful. Numerous preclinical studies of the combination of TNF and INF-gamma have documented their synergistic antitumor effects. These studies show that, even when tumor cell lines are minimally sensitive to either single agent, the combination often induces significant growth inhibition. The combination of rINF-gamma and recombinant TNF also can induce synergistic immunomodulatory effects such as upregulation of HLA-DR antigen on tumor cells. Clinical trials are underway to define the antitumor and immunomodulatory activity of this particular combination.

There is a strong rationale for combining BRMs with other modes of cancer therapy such as radiation or surgery. Agents acting by way of indirect immune-mediated mechanisms likely will have their maximal effect in the setting of minimal tumor burden. This allows optimization of immune-effector to target-cell ratios and elimination of the immunosuppressive effects of large tumor burdens. Combined-modality, adjuvant-therapy trials, involving combinations of BRMs and convention modes of cancer treatment, are now in progress to test these hypotheses.

In conclusion, we must continue to implement not only direct, but also the indirect effects of BRMs -- efforts which depend on an increasing understanding of the immune system. One of the most important directions of future is likely to be combination therapy, which only recently has begun clinical evaluation. Hopefully, with these approaches, we will be able some day to reproduce the antitumor effects, which Coley first observed, and thereby reach our goal of extending and improving patients' lives.

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GROWTH-FACTOR INVOLVEMENT IN THE BIOLOGY OF SOLID TUMORS*

R.N. BUICK, Ph.D.**, *Toronto, Ontario*

Control of cell proliferation is mediated in a tissue-specific fashion in part by a system of regulatory molecules, produced locally or systemically, and acting through specific cell-surface receptors. Such growth-factor systems can be viewed, biochemically, as consisting of three components: the growth factor itself, the receptor molecules, and proteins involved in signal transduction allowing the activated growth-factor receptor to elicit a proliferative response through altered gene expression. In recent years, several workers have implicated such normal growth regulatory processes in carcinogenesis by demonstrating that many retroviral oncogenes are related to normal cellular gene-encoding components of these growth-factor systems.

The recent literature provides a variety of examples of specific abnormalities in such systems that are related to the growth of a number of types of human solid tumors. For convenience, these can be categorized in relationship to the three biochemical components of the growth regulatory system.

Growth Factors

-Transforming growth factor alpha (TGF-α) and transforming growth factor beta (TGF-β) are secreted by many tumors in vivo and by transformed cell lines in culture. They act co-operatively to allow anchorage-independent growth of normal fibroblasts in tissue culture. TGF-α is closely related to epidermal growth factor (EGF) and acts through the EGF receptor; the biological affects of TGF-α can be blocked by antibodies to the EGF receptor demonstrating an autocrine growth regulation. TGF-α, a distinct polypeptide, acts through a specific receptor. In some normal epithelial cells, TGF-β is an inhibitor of growth and inducer of differentiation. This fact has led to the hypothesis that transformation also may be related to loss of expression of TGF-β or its receptor.

-Platelet-derived growth factor (PDGF). The beta-chain of this molecule is identical to the transforming protein of simian sarcoma virus (SSV) – p28v-*sis*. SSV-transformed cells secrete a PDGF-like molecule. Certain tumors, e.g. glioblastomas, also secrete PDGF-like molecules and have PDGF receptors, implying an autocrine growth regulatory loop.

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*Abstract of a paper presented at the 11th Clinical Cancer Research Conference, held on September 28-30, 1987, at Geneva Park, Lake Couchiching, Ontario

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-Fibroblast growth factor (FGF). The Int-2 gene (activated in MMTV-induced mammary carcinoma) is homologous to the FGF gene family. In addition, a gene, identified as a transforming gene from Kaposi's sarcoma DNA, also is a member of the FGF family.

-Bombesin. Small cell lung cancer cell lines produce bombesin which can act as an autocrine growth factor.

Growth Factor Receptors

-EGF receptor. The transforming gene, *erb*-B, is homologous to the gene encoding the EGF receptor. Frequently the receptor gene is overexpressed in human tumors; the primary mechanism acts through gene amplification. Tumor types include squamous carcinoma (head and neck, cervix), glioblastoma and breast carcinoma.

-*Neu*-gene product. The *neu* oncogene, which was isolated by transformation with rat neuroglioblastoma DNA, is related to the *erb*-B oncogene; thus, it is thought to encode a type of receptor similar to the EGF receptor. However, the specific ligand for this receptor has not been identified. The gene is amplified and overexpressed in a high proportion of human breast cancers; the degree of overexpression is related to survival time and time to relapse.

Signal Transduction Components

The products of the *ras* genes have been implicated in signal transduction because of their structural relationship to G-proteins and biochemical evidence of GTP-ase activity. Nuclear oncogene products, e.g. *myc*, *fos*, are expressed transiently after exposure to growth factor. It is possible that, in the absence of growth factor, overexpression or structural alteration of such proteins might activate the signal transduction process. This suggestion is supported by the observation that a high proportion of human tumors, e.g. colon carcinoma, breast carcinoma, neuroblastoma, small cell lung cancers, demonstrate either *ras* or *myc* activation or overexpression.

Taken together, all these examples demonstrate that normal, tissue-specific, growth-regulatory systems are a major target for molecular changes during carcinogenesis, and strongly suggest that such changes underlie the malignant process. As more information becomes available about specific growth-regulatory systems in normal tissues and about common deficiencies in the corresponding malignancies, it should be possible to design therapeutic approaches aimed at imposing normal growth regulation on malignant cells.

REGIONAL CANCER CENTRES

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REGIONAL CANCER CENTRES

The Ontario Cancer Foundation was established in 1943 by an Act of the Ontario Legislature to conduct a program of research, diagnosis and treatment in cancer. The Foundation works in three fields: service, research and education. From its inception, the Foundation has accepted responsibility for:

- the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or special facilities; and
- the maintenance and operation hostels in connection with its treatment centres.

The Foundation also has the most important duty of co-ordinating facilities for cancer treatment and ensuring the adequate reporting of cases and the recording and compilation of data.

The Foundation with its eight Regional Cancer Centres -- Hamilton, Kingston, London, Ottawa, Sudbury, Thunder Bay, Toronto-Bayview, and Windsor – provide facilities for undergraduate and postgraduate study, training of technical personnel, and research fellowships to increase our knowledge about cancer.

The Foundation is distinct from but co-operates with the Ontario Cancer Institute incorporating the Princess Margaret Hospital in the investigation and treatment of cancer and works closely with the Canadian Cancer Society Ontario Division.

The Foundation hopes that *Cancer in Ontario* will assist the practising physician in some of the following ways:

- help him/her become familiar with the various services of the Foundation and its Centres;
- encourage effective patterns of referral and to promote efficient geographical use of the Regional Cancer Centres;
- encourage the individual physician to consult informally with staff members at the Regional Cancer Centre;
- make the resources of the Foundation more widely available to the people of Ontario by increasing the number of contacts between physicians, particularly those outside metropolitan areas, and the OCI/PMH and the Foundation's Regional Cancer Centres.

We urge any physician who reads *Cancer in Ontario* to make suggestions concerning the improvement of cancer control in Ontario. These may be transmitted to the Director of the nearest Regional Cancer Centre or sent directly to the Executive Director, Dr. J.W. Meakin. The Directors of the Regional Cancer Centres may be contacted as follows:

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B. Rigby, B.Sc.N., M.H.Sc.

Manager of Health Records:
D. Armstrong

Lodge Supervisor:
C. Stewart, R.N.

The year 1987 was one of sustained growth at the Hamilton Regional Cancer Centre.

Dr. Ian Hodson was appointed Head of Radiation Oncology for the Centre. Drs. A. Whitton and J. Sathya joined the staff as radiation oncologists.

Dr. James Gowing, who has been appointed to co-ordinate the Community Cancer Clinic Network for Central-West Ontario, is based part-time at the Centre. The network includes clinics at Brantford, Burlington, Cambridge, Guelph, Hamilton, Niagara Falls, St. Catharines and Welland. This network interacts with existing institutions to provide tertiary cancer care at the community level.

The Hamilton Centre's teaching program has been enhanced. The Royal College has recognized McMaster University's training program in medical oncology. Dr. Andrew Arnold is program director. Dr. William Muirhead continues as director of the postgraduate training program in radiation oncology. Recruitment is underway to fill residency slots.

Clinical and basic research is continuing at the Centre. Medical and nursing staff maintain their participation in a variety of clinical trials.

A number of the medical staff, in collaboration with the Centre's scientists and their university colleagues, continue to participate in laboratory-based research. This work, which is focussed mainly at the basic-clinical interface, includes: (1) development of in vivo assays to assess tumor response to radiation and/or cytotoxic drugs; (2) in vitro cytotoxicity studies of clinical chemotherapeutic drugs; and (3) in vitro and in vivo studies of the interaction of hyperthermia with other cytotoxic drugs or with radiolabelled monoclonal antibodies.

We are carrying out internal renovations to accommodate our increasing patient load, are continuing to acquire office space, and are getting on with the planning for the new facility. Construction is now scheduled to begin in late 1988.

B. Rigby, B.Sc.N., M.H.Sc.
Co-ordinator, Cancer Information Services

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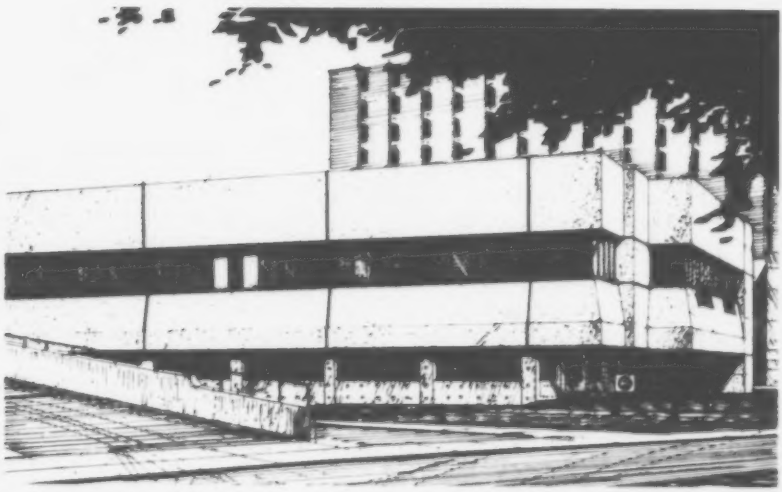
KINGSTON REGIONAL CANCER CENTRE

KINGSTON GENERAL HOSPITAL



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A. Voino, R.N.

Chief Technician:

N. Hobbs

Social Service Nurses:

R. Crafts, Reg.N.
C. Keith, Reg.N.

Manager of Health Records:

TBA

Lodge Supervisor:

D. Broeders, Reg.N.

The past year has brought several favorable developments in cancer research at Queen's University and the Kingston Centre.

The university has created the Stauffer Chair of Cancer Research and Dr. Roger Deeley was appointed to fill this chair. He is recruiting two additional scientists and all expect that his group and the OCTRF career scientists and clinical scientists will work in close co-operation. Already through the good offices of Dean Wilson, Associate Dean Clarke and Dr. Deeley we have achieved geographic propinquity, and the 3rd floor of Botterell, the Medical Sciences Building at Queen's University, has been dedicated to cancer research. We are in the fortunate situation where cancer research is conducted from "bench to community". Clearcut and meaningful interaction exists between the various groups of research workers, and important liaisons are developing between faculty from different departments, and indeed different universities. Furthermore, this research has been highly productive: during the year, members of our Centre have published 57 articles.

Drug resistance and experimental cancer therapy are of great interest to several of our scientists and have become central themes. Thus, Dr. Susan Cole continues her studies with monoclonal antibodies; she is exploring their role in the identification of resistant cell lines in situations where the resistance is clearly different from that due to P-glycoprotein. She has collaborated with Dr. Bruce Elliott in the evaluation of major histocompatability antigens in lung cell lines maintained in tissue cultures, and the study of the modifications they undergo following exposure to chemotherapeutic agents and in the development of drug resistance.

Dr. James Gerlach, who joined our Centre in July 1987, continues his work on multidrug resistance, which is related to P-glycoprotein.

Dr. Barbara Campling is one of two clinicians in the OCTRF system who holds the appointment of "clinician scientist". She continues her studies which employ MTT in a technique that rapidly determines the chemosensitivity of fresh tumor samples; then she determines whether this sensitivity correlates with the patient's responsiveness to chemotherapy.

Dr. William Mackillop is studying the interaction between hyperthermia and response to cytotoxic drugs.

Dr. James Kennedy continues his studies on photochemotherapy -- both basic and applied -- in collaboration with Dr. Roy Pottier of the Royal Military College in Kingston.

Since the promotion to Head of the Department of Microbiology and Immunology, Dr. Hugh Pross has maintained a cross-appointment with our Centre and thus has continued his work on natural killer cells.

The NCIC Clinical Trials Program is based in Kingston under the direction of Dr. Joseph Pater. The Kingston Centre participates actively in a number of NCIC clinical trials. Dr. Elizabeth Eisenhauer, medical oncologist, directs the new drug program. Dr. Peter Dixon, radiation oncologist, now has a 50% appointment with the NCIC Trials Group. Dr. Wyecliffe Lofters is the Centre's co-ordinator.

In the area of behavioral research, Dr. W.J. Mackillop is investigating: Patients' perceptions of the nature of their illness and the intent of their therapy; methods to define the information which patients should be given before they are asked to consent to treatment (with Dr. Pater); and methods to evaluate the ethical acceptibility of specific clinical trials in oncology (with Dr. Robert Steele of Department of Community Health at Queen's University and Dr. Brian O'Sullivan of the OCI/PMH in Toronto).

Our Centre has initiated a series of studies with Drs. P.M. Cameron and L. Sheldon – in the Department of Psychiatry – on depression in cancer patients; and with Dr. M. Condra (Department of Psychology) on the value of "groups". We also have begun to study the impact of staff support groups with Mrs. Lucille Groll (Department of Psychiatry); and with Dr. J. Pater and Elaine vanMelle (Department of Epidemiology) we are reviewing supportive care and psychosocial programs in Ontario.

Finally, we are working closely with Information Systems at Head Office, especially George Boc, Ed Murphy and June Murphy, in an attempt to adapt the Honeywell program to Medlog programs so as to audit and analyze patient data already in the central computer.

A.D. Ginsburg, M.D., F.R.C.P.(C)
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LONDON REGIONAL CANCER CENTRE

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A. Akinradewo, Ph.D.
D.J. Dawson, Ph.D.
J. Schroeder, M.Sc.

Career Scientists:

A. Chambers, Ph.D.
J. Harris, Ph.D.
W.R. Inch, Ph.D.
D.J. Koropatnick, Ph.D.

Terry Fox Fellow:

A. Tuck, M.D.

Administrator:

M.J. Morrison, M.P.A.

Business Manager:

T.B.A.

Nursing Co-ordinator:
W. Gillis, B.Sc.N.

Social Worker:
A. Sawarna, M.S.W.

Senior Radiotherapy Technologist:
P. deSilva, R.T.T.

Manager of Health Records:
D.G.E. Ross, C.C.H.R.A.

Lodge Supervisor:
C. Sellery, B.Sc.N.

In the year 1987, we bid farewell to Dr. Haydn Bush who resigned as Director to pursue other academic challenges. Dr. Bush's departure has left a real hiatus; the changes he introduced during his seven-year tenure will continue to have a significant impact on future developments.

Dr. Leslie Levin became the new Director of the London Regional Cancer Centre on April 1, 1987.

Most of the activity at the Centre during the past year has been directed towards our relocation to the Westminster Campus, which is scheduled for April 1988. We are entering a particularly exciting phase because relocation presents the unique opportunity to revise existing operations, and introduce a variety of changes. The staff has shown an exemplary capacity and willingness to generate and introduce these changes.

Construction of the new Centre is proceeding well on schedule, and as this report is being written, the bases are being installed for the new radiotherapy machines.

The past year has shown an increasing emphasis on oncology education and Mrs. Shelley Markland has led in the introduction of a rapidly expanding new program aimed at health-care professionals. This effort has had numerous "spin-offs" -- the most significant of which is the expression of increased commitment to our extensive outreach program.

Dr. Jamie Skillings has been appointed Chairperson of a Cancer Screening Advisory Panel, which will produce guidelines for cancer screening in Southwestern Ontario in conjunction with the Canadian Cancer Society and the Faculty of Medicine, University of Western Ontario. The analytical dietary intervention research, which was initiated last year, has completed its first study; we hope to expand its scope to include the role of vitamin A in tumor differentiation.

The new Centre has generated renewed support for our research which will likely be given a major boost by the University of Western Ontario, Victoria Hospital and the OCTRF's Research Advisory Panel. We hope that this consortial arrangement will provide the infrastructure for the rapid expansion of cancer

research in this area. Furthermore, as a result of negotiations with the Dean of Medicine, University of Western Ontario, the new Centre will be recognized as an important focus for academic oncology in London.

Clinical research continues to be a major activity in this Centre; in this regard, the Clinical Trials Unit, under the direction of Dr. Vivien Bramwell, has been extremely productive.

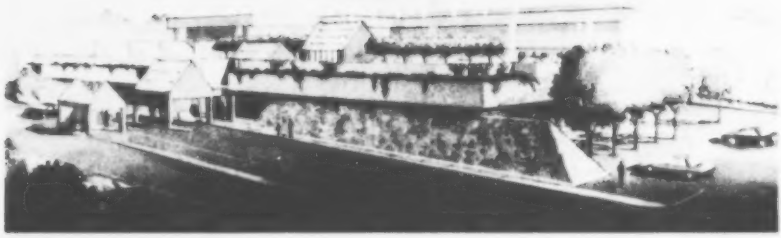
Among the staff additions and changes during the year we are pleased to note the following: In June, Dr. Vivien Bramwell became Head of Medical Oncology, all wish her the best in this important role; Drs. Leo Houghton and Hugh Prichard are our new radiation oncologists; Dr. A. Akinradewo was appointed as a physicist; we welcomed Richard Sourkes to the Department of Social Work; Eunice Anderson is the new program co-ordinator in the Department of Nursing; and Dianne Goettler is the new dietitian on staff.

As the time for relocation draws nearer, the initial anxiety is giving way to tremendous excitement: we all feel privileged to be part of this historical event.

L. Levin, M.D., F.R.C.P.(C)
Director

NORTHEASTERN ONTARIO ONCOLOGY PROGRAM

LAURENTIAN HOSPITAL, SUDBURY



Director:

R.E.T. Corringham, M.B..B.S.

Medical Oncologists:

T. Bozek, B.M..B.Ch.
G.D. Goss, M.B..B.Ch.
C.L. Sinnof, M.B..B.Ch
M.D. Vincent, M.B..Ch.B.

Clinical Assistant:

G.M. Kane, M.B..B.Ch.

Epidemiologist:

V. Nguyen, Ph.D.

Psychologist:

S. Steggles, M.A.

Administrator:

A. Pabani, M.B.A.

Nurse Administrator:

C. McChesney, B.Sc.N.

Manager of Health Records:

R. Zambelli, C.C.H.R.A.(C)

Definitely, 1987 has been a better year for the Northeastern Ontario Oncology Program (NEOOP). With the arrival of Dr. Gabrielle Kane from the PMH in January and of Dr. Mark Vincent from the U.K. in April, we were able to reopen our clinical program to new referrals; now with the arrival of Dr. Clive Sinoff from South Africa and Dr. Thomas Bozek from U.K., we are expanding our services to meet the needs of the Northeastern region. With Dr. Meakin in attendance, we have met with health-care representatives from North Bay, Sault

Ste. Marie, and Timmins to discuss the establishment, across the region, of a network of community cancer centres, supported by the new Northeastern Ontario Regional Cancer Centre to decentralize cancer treatment, particularly chemotherapy and palliative care. In concert with this initiative, we are also participating in the PMH's outreach program to the North-East, and jointly staff the PMH clinic in Sudbury and intend to expand this activity to the other PMH regional clinics.

In April 1987, our temporary office space was opened by the Minister of Health the Hon. Murray Elston. This has freed up more space for clinical use. The plans for the new Centre have been completed and construction began in December 1987; assuming no delays and adequate funding for the OCTRF's one-third of the costs through the Cancer Care Fund, we expect its completion in 24 months.

Claire McChesney, our nurse administrator, has been working diligently to enhance the Nursing Department. Mehbs Manji, our new supervisor of computer services, has efficiently computerized the entire NEOOP. Dr. Shawn Steggles, who has attained his Ph.D. in psychology, is developing a busy psychosocial program. Dr. Van Nguyen, our epidemiologist, has produced some useful epidemiological studies relating to the North-East region. The resultant data will be used to plan further development of services. Also we hope to initiate studies into prevention, particularly with regard to cancer of the cervix and breast.

Our research efforts have expanded with the establishment of a clinical trials office and a library. As well as participating in NCIC and OCOG clinical trials, we have also begun our own in-house studies. We are still working collaboratively with Laurentian University to establish a clinician scientist program.

We have assisted in the establishment of a Palliative Care Foundation in Sudbury and are working closely with local family practitioners to enhance medical care for palliative patients. We are expanding our educational programs; over 100 health-care professionals attended our annual two-day Cancer Update, which again included a nursing workshop. Out-of-town guest speakers came from the OCTRF Toronto-Bayview and Ottawa Regional Cancer Centres, and the Princess Margaret, Mount Sinai and Toronto General Hospitals.

We have completed planning for the new Centre and construction was begun in November 1987. We expect the Centre to be completed in 1989 and fully operational in 1990. The radiation equipment has been ordered and staff recruitment has commenced.

The NEOOP is beginning to achieve its objective of providing first-class care for cancer patients and recruit the human resources needed to operate the new cancer centre; this new centre will extend cancer care across the Northeastern Ontario region, through the hard work and dedication of its staff supported by the OCTRF, the Ministry of Health, and the Sudbury hospitals. However a great deal of work still remains to be done to achieve the range and depth of resources needed to create a centre of excellence for the Northeastern region.

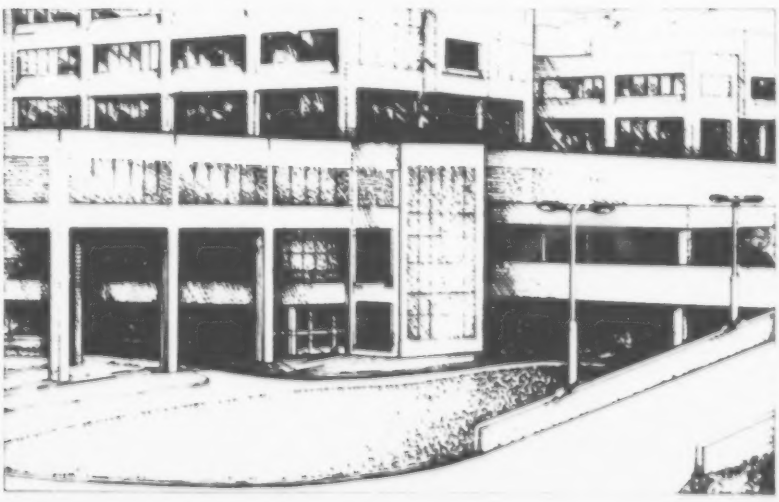
R.E.T. Corringham, M.B.,B.S.
Director

OCF

OTTAWA REGIONAL CANCER CENTRE

OTTAWA CIVIC HOSPITAL

AND OTTAWA GENERAL HOSPITAL



Director:

G.E. Catton, M.B. B.S.

Radiation Oncologists:

J. Crook, M.D.
C.J.E. Danjoux, M.D.
L. Eapen, M.D.
B. Esche, M.D.
P. Genest, M.D.
A.L. Girard, M.D.
R.S.R. McDermot, M.D.
B.D. Nair, M.B. B.S.

Medical Oncologists:

S. Aitken, M.D.
C. Cripps, M.D.
W.K. Evans, M.D.
D. Logan, M.D.
J.A. Maroun, M.D.
D.J. Perrault, M.D.
D.J. Stewart, M.D.
S. Verma, M.D.
V.P.J. Young, M.D.

Clinical Assistants:

H. Bastianelli, M.D.
J. Blakslee, M.D.
K.R. Hopkinson, M.D.
S. McKim, M.D.
K. O'Toole, M.D.
I.A. Prosser, M.D.
K. Robillard, M.D.
K. Wells, M.D.

Career Scientists:

H.C. Birnboim, M.D.
R.G. Liteplo, Ph.D.
R. Hawley, Ph.D.

Physicists:

J. Cygler, Ph.D.
L.H. Gerig, Ph.D.
P.C. Johns, Ph.D.
R.M. Kroeker, Ph.D.
P.M. Pfalzner, M.Sc.
G.P. Raaphorst, Ph.D.
M. Soubra, M.Sc.

Administrator:

M.L. Trickey, M.B.A.

Business Manager:

S. McAdam

Executive Secretary:

D. Pineau, C.M.S.

Nurse Administrator:

C.J. MacMillan, B.Sc.N.

Head Nurse (General Division)

L. Fawcett, R.N.

Senior Radiotherapy Technician:

R.P. Wallace, A.C.R.T.

Managers of Health Records:

M.C. Therrien (Civic Hospital Division)
M.M. Brassard (General Hospital Division)

Lodge Supervisor:

J.M. Davidson, R.N. (Maurice J. Grimes Lodge)
I. Martin, R.N. (Pavillon Alta-Vista Lodge)

As in previous years we have had several staff changes. Two South African physicians – Drs. Heidi Martins and Colin Germond, who are committed to the Northeastern Ontario Oncology Program in Sudbury – joined the medical oncology training program with Dr. Pedro Lopez.

On January 2, Drs. Bernd Esche and Juanita Crook became members of the full-time medical staff in radiation oncology. Dr. Diane Logan began as clinician scientist in July sited in Prof. C-Y Kang's laboratory in the Department of Microbiology and Immunology at the University of Ottawa. Dr. Susan Aitken joined the full-time medical staff in medical oncology in August.

Drs. James Blakslee and Susan McKim are new clinical assistants in radiation oncology replacing Drs. Brenken and Goldsman. Dr. Karen O'Toole came on staff as a clinical assistant to the inpatient service of medical oncology at the Civic Division, and Dr. Mary Wells joined the staff at the General Division as clinical assistant in medical oncology.

Dr. Barbara Fisher will spend a research year in hyperthermia, both clinical and "wet" laboratory, at Stanford University Medical Centre on a Gordon Richards Fellowship. After this study she plans to return to one of the OCTRF centres to continue her work.

Dr. Robert Liteplo, career scientist in experimental oncology, received a three-year award from the National Cancer Institute of Canada. The award provides for an extension of his research on tumor progression and metastases. Dr. Liteplo has a cross-appointment in the Department of Biochemistry, University of Ottawa, where he will contribute to their teaching program.

Mr. Milton Trickey became the administrator at the Ottawa Centre, effective November 2. After receiving his B. Comm. and M.B.A. from the Sir George Williams University in Montreal, he took the Hospitals of Ontario Management Course through the Canadian Hospital Association.

Wanda Assang again received the Maurice Legault Scholarship Award and is now in the second year of her Master's degree in nursing at McGill University.

In Lisbon in June, Dr. Juanita Crook won the prize for the best poster presentation at the sixth annual meeting of the European Society of Therapeutic Radiology and Oncology. She made two presentations at the poster session "Definitive irradiation for early-stage carcinoma of the soft palate and uvula: the indications for iridium-192 implantation", and "Intracavitary irradiation of the nasopharynx by a mould technique". The prize was free airline tickets to the next meeting of ASTRO to be held in Amsterdam.

The third career scientist, Dr. Robert Hawley, came on staff in October. He brings to the Department of Experimental Oncology a research interest in molecular immunology and control of lymphocyte differentiation. He will be setting up colonies of immunodeficient mice and will be introducing genes into cells from these animals by using specially constructed retroviruses.

In November the General Division celebrated the beginning of a new era when it began installation of a Siemens-KD2 linear accelerator.

The new 30-bed Pavillon Alta Vista Lodge, on the 7th Floor of the Ottawa General Hospital, accepted its first patient on August 24. The official opening ceremonies took place on September 10. The guest of honor at the opening ceremonies was the Hon. Bernard Grandmaitre, Minister of Revenue and Minister responsible for Francophone Affairs.

Construction of the Maurice Grimes Lodge expansion continues with a scheduled completion date late in 1988.

A Siemens Magnetom MR unit, Tesla 1.5, was installed at the Ottawa General Hospital and began imaging in August.

New members in the Department of Medical Physics are: Dr. Randall Kroeker -- magnetic resonance imaging physicist; Mr. Mazen Soubra -- radiation physicist from Winnipeg; and a new trainee, Dr. J. Szanto. Strong service and research programs are being developed in these areas, e.g. we have started a cellular therapeutic biophysics program. Two Ph.D. students joined the medical physics program and this has strengthened the research and academic connections with the medical physics section of the Department of Physics, Carleton University.

The biophysics laboratory is doing research on the effect of hyperthermia alone or in combination with radiation or chemotherapy on various cell lines. Hyperthermia research in pigs is carried out at the National Research Council of Canada [NRC(C)]. Research is being carried out on the effect of irradiation on brain tumors in animals, using the MR imaging spectroscopic facilities at the NRC(C).

Mrs. Manon Lacelle, R.T., received the Percy Ghent Memorial Award of the Ontario Association of Medical Radiation Technologists for her paper "Its up to you, little pions". Miss Sharon Gay, R.T., received the Mallinckrodt Award of Excellence of the Canadian Association of Medical Radiation Technologists for the highest aggregate achieved by a student in the final C.A.M.R.T. certification examinations.

Drs. Libni Eapen and Annette O'Connor of the University of Ottawa School of Nursing and the radiation oncology nursing staff carried out a prospective study on "Decision making about smoking cessation following the diagnosis of head and neck cancer".

G.E. Catton, M.B., B.S., D.M.R.T., F.R.C.P.(C.)
Director

OCF

THUNDER BAY REGIONAL CANCER CENTRE

GENERAL HOSPITAL OF PORT ARTHUR

Director:
J.F. Kotalik, M.D.

Radiation Oncologists:
S. Gulavita, M.B.,B.S.
M. McLean, M.B.,B.Ch.

Medical Oncologist:
H.S. Dhaliwal, M.D. *(locum)*

Clinical Associate in Palliative Care:
J.A. Chalykoff, M.D.

Clinical Assistant:
L. Pratt, M.D.

Physicists:
M. Al-Ghazi, Ph.D.
P.D. Sharma, M.Sc.

Business Manager:
M.M. Ryan

Nurse Administrator:
L. Bright, Reg.N.

Manager, Radiation Therapy:
J.V. Morgan, R.T.

Manager of Health Records:
C. Alexson, C.C.H.R.A.(C)

Lodge Supervisor:
M. Magnusson

The year of 1987 brought further staff changes. After serving two years in the Centre and contributing greatly to the development of its clinical trials program, Dr. Donald Zaentz has resigned to resume the private practice of medical oncology in the USA. In the meantime, his practice here has grown to the point that we require two medical oncologists. Recruitment has started but, as yet, no physicians have been found for these positions. Dr. Jonathan Yau from Edmonton served as a locum during the summer and Dr. H.S. Dhaliwal, a medical oncologist from St. Bartholomew's Hospital in London, worked here for several months. Dr. Dhaliwal also was appointed Visiting Professor of McMaster University and spent some of his time at the Hamilton Regional Cancer Centre. Dr. Lynn Pratt joined us from Winnipeg as our part-time clinical assistant. Dr. Judi Chalykoff continues as a part-time clinical associate in palliative care. Mr. Dale Anderson joined us as computer systems manager, and Miss Carol Alexson is the new manager of the Health Records Department.

Staff shortages continue to plague this Centre. Currently we have an opening for two medical oncologists, a clinical trials nurse, a pharmacist and a clinical psychologist. This last would be a joint appointment with the Department of Psychology of Lakehead University.

Throughout the summer we had an Ivan H. Smith summer student from Queen's University and, on Harold E. Johns Summer Studentships, two physics students from Lakehead University. We expanded our scope of service by adding Sioux Lookout clinic and are exploring the possibility of further clinics in Terrace Bay and Hearst.

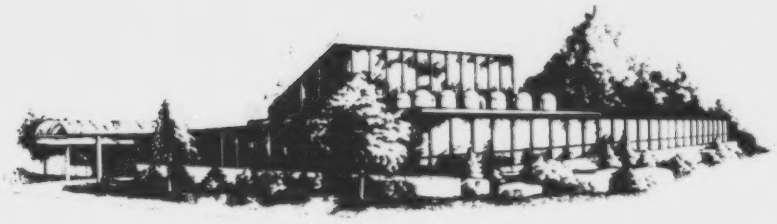
Space in the Centre is at a premium and we could accommodate new staff and new programs only by expanding into the lodge. The business office moved into the Amethyst House – into larger renovated facilities, vacated by the Canadian Cancer Society. We have asked for permission to start planning for substantial Centre expansion – a process which will be co-ordinated with the expected major expansion of our host hospital. We expect that this expansion will incorporate a special oncology unit. At present, cancer patients are placed in any available bed in a medical or surgical ward. Continuous effort will be needed to strengthen our staff and to make maximum use of available space optimization; only by so doing can we cope with increasing demands for service and also make a contribution to cancer research.

J.F. Kotalik, M.D., D.M.R.T., F.R.C.P.(C)
Director

OCF

TORONTO-BAYVIEW REGIONAL CANCER CENTRE

SUNNYBROOK MEDICAL CENTRE



Director:

R.D.T. Jenkin, M.B.,B.S.

Radiation Oncologists:

I. Ackerman, M.D.
J.M. Balogh, M.D.
M.P. Berry, M.B.,B.S.
Ch.N. Catton, M.D.
P.A. Catton, M.D.
M.A. Doherty, M.B., B.S.
R.G. MacKenzie, M.D.
N.D. Mountifield, M.D.
C.S. Young, M.D.

Medical Oncologists:

R.A.A. Buckman, M.B.,B.Ch.
N.A. Iscoe, M.D.
I.J. Kerr, M.D.
K.I. Pritchard, M.D.
J.J. Rusthoven, M.D.
D.J.A. Sutherland, M.D.

Clinical Assistants:

H.M. Kocandrle, M.D.
H.I. Reiter, M.D.
L. Vokac, M.D.
J.M. Wall, M.D.
A. Wilk, M.D.

Physicists:

R.B. Barnett, Ph.D.
H.B. Michaels, Ph.D.
P.F. O'Brien, M.Sc.
R.A. Siwek, Ph.D.

Administrator:

H.B. Wodinsky, M.H.Sc.

Administrative Assistant:

K.A. Nicholson

Finance Manager:

A. Smith, B.A.

Nurse Administrator:
C. Johnston, Reg N

Chief Radiotherapy Technologist:
S.V. Scott, A.C.(T.) R.T.R.

Manager of Health Records:
M. Mistruzzi, C.C.H.R.A.(C.)

1987 has been a year of strategic decisions at the Toronto-Bayview Regional Cancer Centre. Early in the year, at the request of the Minister of Health, a "factfinder", Mr. Alan Backley, examined the status of oncology in the Metropolitan Toronto region. Subsequently the Minister announced that the new Princess Margaret Hospital (PMH) would be built on University Avenue; a second "Backley Committee" was appointed to examine the effect of this relocation on the university hospitals.

The Ministry of Health announced: That the new PMH would be designed to accommodate 7000 new patients annually; that the Toronto-Bayview Centre would continue to provide services for the increasing number of cancer patients in the Metropolitan Toronto region until 5000 new patients were accrued annually, approximately by 1991/92; and that planning could commence for new OCTRF cancer centres to serve the West and East Metropolitan Toronto regions.

Therefore the Toronto-Bayview Centre is planning to double in size. In as much as we have outgrown our resources, our facility short fall increases daily and there is an urgent need to construct the new centre as soon as possible. For example, we met the needs of 3300 new patients in 1987 compared to our planned size of 2500 new patients: our linear growth will continue. Even though we commissioned a fifth radiation treatment machine, a cobalt unit, in October 1987, our waiting list for radiation treatment remains excessive: some patients wait as long as six weeks for non-emergency treatment. Now the limiting factor in reducing these waiting lists to an acceptable level is our ability to recruit an adequate number of radiation technologists. Our decision to open a school for radiation technologists, in association with the University of Waterloo, may provide a long-term solution to this immediate problem.

The continuous expansion of the oncology program at Sunnybrook Medical Centre (SMC) has major resource implications for the hospital. Oncology bed numbers and the oncology component of all the diagnostic and support services will need to double. SMC is planning a major frontal expansion, which *inter alia* will provide new beds for cancer patients.

A major step toward oncology laboratory research is nearing reality. Adjacent to the Toronto-Bayview Centre and scheduled to open in 1989, the SMC is developing a research tower which will house a focussed oncology research group. For seven years we have endured the presence of "shelled in" research space in our building, which was never completed. This long delay will be justified if we are able to assemble a stronger research team in the new, larger research facility.

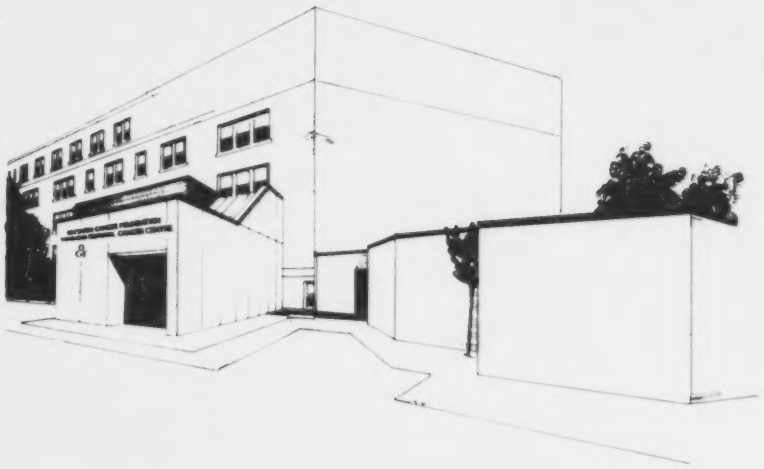
The hard work necessary to turn these plans into reality has begun in earnest: already various groups are generating sections of the new functional program for the Toronto-Bayview Regional Cancer Centre.

D.T. Jenkin, M.B. B.S. F.R.C.P.(C)
Director

OCF

WINDSOR REGIONAL CANCER CENTRE

METROPOLITAN GENERAL HOSPITAL



Director:

G.C.K. Mok, M.D.

Radiation Oncologist:

C.D. Springer, M.B.,B.S.

Medical Oncologists:

H.T. Abu-Zahra, M.B.,B.Ch.
Z.Y. Alam, M.B.
D.A. Sicheri, M.D.
S. Yoshida, M.D.

Clinical Assistants:

M. Foote, M.D.
P. Smith, M.D.

Physicist:

K.S. Chang, Ph.D.
D. Smocovitis, M.Sc.

Business Manager:

E. Schwindt

Senior Radiotherapy Technician:

R. Macpherson Todd, R.T.

Senior Nurses:

M. O'Neill, Reg.N.
S. Vickers, Reg.N.

Manager of Health Records:

R. Van Der Borgh

The year 1987 brought several staff changes to the Windsor Centre. In March, Dr. Yasmin Alam joined our medical oncology department. In May, our clinical assistant in medical oncology, Dr. Patrick Smith, left the Centre to start general practice. In mid-July, Dr. Dolores Sicheri became the fourth medical oncologist; she came from the University of Oklahoma Health Science Centre, where she practised for four years. Dr. Jim Gilchrist, radiation oncologist, who left the London Regional Cancer Centre and went to Ethiopia a year ago, returned to Canada in late July. For three months he worked as a *locum tenens* in the radiation oncology department in our Centre. In early August, Dr. Kai Siung Chang, medical radiation physicist, joined our staff.

Installation of the dual-energy Philips SL25 linear accelerator was completed this spring. The unit was accepted on June 1. Acquisition data is being compiled for treatment planning and we anticipate that the unit will be commissioned by the end of the year.

In May our host hospital received approval from the Ministry of Health for the installation of a CT scanner. We expect the unit to be installed in the summer of 1988. A new computer will be required in the Centre to assist treatment planning with the CT scanner.

The Windsor Centre is suffering from a severe shortage of working space. To provide even a small office for our newly appointed senior radiation therapy technologist, we had to partition the existing physics laboratory, thus reducing further the already inadequate space in the Department of Physics. The existing office for the physicist is too small for two physicists. The Health Records Department occupies an area that was leased from the host hospital as a temporary measure. By agreement, we have to vacate this space with a six-month's notice. Because we have no storage space, we must send out many patient records for commercial storage in the city. It is costly to send for these charts when they are needed and costly to return them for storage, to say nothing of the inconvenience. The Centre has no storage room. Equipment is stored in the small mould and photography room and some corridors, thus creating traffic obstacles. The examination rooms in the Department of Radiation Oncology are small and there are only a few of them. This department also is understaffed. We must recruit additional radiation oncologists if we are to provide adequate patient service now and in the future. We have no research laboratory or offices for research workers. Also we need office space for psychosocial service, screening and cancer detection programs and for a nutritionist. The Centre has had three renovations and expansions during the past 20 years. According to the consultant architect, it is no longer possible to expand further from the present premises. To meet the challenge of the next decade we need a new, larger cancer centre in Windsor.

G.C.K. Mok, M.D.
Director

SERVICE LOAD

The following tables describe the service load of the Foundation's seven regional cancer centres and the Northeastern Ontario Oncology Program in Sudbury during the calendar year 1986.

In 1986, 48,298 patients were seen at these centres. Of these, 92% had malignant lesions and, of these lesions, 14,042 were new to the centres (Table I). Of cases referred for non-malignant conditions, 86% were first seen in 1986 (Table II). The majority of these, 2,013, were seen in consultation. In all, 10,613 cancer cases were treated by radiotherapy (Table III); of these, 4,733 were treated by cobalt units, 4,779 by a linear accelerator, and 1101 by other methods of radiotherapy.

During the year, patients made 488,550 visits to the regional cancer centres and the majority, 475,989, were for treatment of malignant disease (Table IV). Of all radiation treatments, 86% were given on an outpatient basis (Table V).

As of January 1, 1982, with the implementation of the Patient Care Management System (PCMS) in the centres, it has been possible to retrieve data in more detail than was possible in previous years. The current tabulations are taken from data as of September 1987. It must be emphasized that these tables are comparable only with the service load tables published for 1982, 1983, and 1984 and 1985; they are not comparable with those for the years before PCMS was implemented.

TABLE I

Malignant Caseload During 1986*

TREATMENT CENTRE	TREATED				Seen for Consultation or Follow-up	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy	Procedures		
	Cases New in Current Year					
Hamilton	1,147	191	467	37	1,242	3,084
Kingston	539	107	119	14	370	1,149
London	891	289	394	143	956	2,673
Ottawa	958	193	396	110	1,136	2,793
Sudbury	–	–	120	4	154	278
Thunder Bay	172	46	86	11	177	492
Toronto-Bayview	983	223	179	342	872	2,599
Windsor	341	85	199	6	343	974
TOTAL	5,031	1,134	1,960	667	5,250	14,042
	Cases Registered in any Previous Year					
Hamilton	443	218	875	27	5,109	6,672
Kingston	183	119	176	19	2,405	2,902
London	344	230	590	203	4,810	6,177
Ottawa	404	336	871	147	6,012	7,770
Sudbury	–	–	165	3	114	282
Thunder Bay	71	47	157	29	977	1,281
Toronto-Bayview	199	123	245	133	1,760	2,460
Windsor	114	95	413	32	2,294	2,948
TOTAL	1,758	1,168	3,492	593	23,481	30,492
TOTAL ALL MALIGNANT	6,789	2,302	5,452	1,260	28,731	44,534

* Includes cases seen at peripheral clinics.

TABLE II

Other (Non-Malignant) Caseload During 1986*

TREATMENT CENTRE	TREATED				Seen for Consultation or Follow-up	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy	Procedures		
	Cases New in Current Year					
Hamilton	28	–	12	12	249	301
Kingston	11	2	53	97	307	470
London	61	3	80	408	555	1,107
Ottawa	27	1	4	118	137	287
Sudbury	–	–	5	–	9	14
Thunder Bay	3	–	11	21	104	139
Toronto-Bayview	11	1	4	196	478	690
Windsor	12	–	19	19	174	224
TOTAL	153	7	188	871	2,013	3,232
	Cases Registered in any Previous Year					
Hamilton	2	–	1	–	23	26
Kingston	2	–	–	2	30	34
London	1	–	3	1	65	70
Ottawa	2	–	1	24	59	86
Sudbury	–	–	–	–	–	–
Thunder Bay	1	–	–	1	9	11
Toronto-Bayview	–	–	1	50	235	286
Windsor	–	–	1	–	18	19
TOTAL	8	–	7	78	439	532
TOTAL ALL MALIGNANT	161	7	195	949	2,452	3,764

* Includes cases seen at peripheral clinics.

TABLE III

Cases Treated During 1986 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO BAYVIEW	WINDSOR	TOTAL
	Malignant Neoplasms							
Superficial x-ray	162	181	80	28	46	61	45	603
Deep x-ray	10	4	–	–	–	–	113	127
Cobalt[60]	1,168	439	573	1,139	222	682	510	4,733
Cesium[137]	–	–	–	–	–	–	–	0
Betatron	–	–	–	–	–	–	–	0
Linear accelerator	789	473	1,417	1,014	130	956	–	4,779
Intracavitary	52	40	88	58	9	22	20	289
Interstitial	14	3	8	19	3	11	0	58
Moulds and applicators	–	–	8	–	–	–	–	8
Systemic isotopes	–	–	–	–	–	–	–	0
Others**	16	–	–	–	–	–	–	16
SUB-TOTAL	2,211	1,140	2,174	2,258	410	1,732	688	10,613
	Other Non-Malignant							
Superficial x-ray	5	4	21	1	3	–	2	36
Deep x-ray	1	–	–	–	–	–	5	6
Cobalt[60]	23	7	8	16	1	4	5	64
Cesium[137]	–	–	–	–	–	–	–	0
Betatron	–	–	–	–	–	–	–	0
Linear accelerator	4	3	18	13	2	8	0	48
Intracavitary	–	–	–	–	–	–	–	0
Interstitial	–	–	–	–	–	–	–	0
Moulds and applicators	–	–	18	–	–	–	–	18
Systemic isotopes	–	–	–	–	–	–	–	0
Others**	–	–	–		–	–	–	0
SUB-TOTAL	33	14	65	30	6	12	12	172
TOTAL*	2,244	1,154	2,239	2,288	416	1,744	700	10,785

* A case can be treated by more than one method per year.
**Others include radiation codes unknown

TABLE IV

Service Load, 1986

TREATMENT CENTRE	VISITS FOR					TOTAL VISITS
	Treatment			Non-Treatment		
	Radiation	Chemotherapy	Procedures	Simulations	Consultation or Follow-up	
	Visits for Malignant Neoplasms					
Hamilton	27,342	14,294	540	2,403	45,967	90,546
Kingston	12,504	2,961	496	1,646	19,901	37,508
London	33,556	8,425	1,425	2,356	42,137	87,899
Ottawa	32,801	11,595	1,494	2,757	59,930	108,577
Sudbury	–	2,069	146	–	8,709	10,924
Thunder Bay	6,487	2,619	677	360	9,466	19,609
Toronto-Bayview	23,402	4,233	1,566	2,246	37,536	68,983
Windsor	11,598	6,766	392	1,199	31,988	51,943
TOTAL	147,690	52,962	6,736	12,967	255,634	475,989
	Other Non-Malignant					
Hamilton	202	29	62	28	623	944
Kingston	159	71	395	18	1,024	1,667
London	466	198	857	24	1,954	3,499
Ottawa	373	13	377	34	796	1,593
Sudbury	–	39	9	–	263	311
Thunder Bay	57	72	93	3	610	835
Toronto-Bayview	146	14	506	12	1,731	2,409
Windsor	121	47	121	19	995	1,303
TOTAL	1,524	483	2,420	138	7,996	12,561
TOTAL ALL VISITS	149,214	53,445	9,156	13,105	263,630	488,550

TABLE V

Treatments by Radiation During 1986, In-Patients and Out-Patients

METHOD OF TREATMENT	HAMILTON		KINGSTON		LONDON		OTTAWA		THUNDER BAY		TORONTO BAYVIEW		WINDSOR		TOTAL	
	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out
	Malignant Neoplasms															
Superficial x-ray	9	753	14	673	53	590	31	242	7	285	2	432	1	469	117	3,444
Deep x-ray	6	21	9	3	–	–	–	–	–	–	–	–	42	952	57	976
Cobalt[60]	1,287	11,267	1,282	4,590	1,724	7,711	2,540	14,047	855	3,385	1,528	6,444	1,516	8,596	10,732	56,040
Cesium[137]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Betatron	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Linear accelerator	913	12,993	730	5,156	4,404	18,958	1,557	14,300	266	1,674	1,582	13,380	–	–	9,452	66,461
Intracavitary	61	–	44	–	100	–	63	–	12	–	22	–	22	–	324	–
Interstitial	14	–	3	–	3	5	21	–	3	–	12	–	–	–	56	5
Moulds and applicators	–	–	–	–	1	7	–	–	–	–	–	–	–	–	1	7
Systemic isotopes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Others*	17	1	–	–	–	–	–	–	–	–	–	–	–	–	17	1
SUB-TOTAL	2,307	25,035	2,082	10,422	6,285	27,271	4,212	28,589	1,143	5,344	3,146	20,256	1,581	10,017	20,756	126,934
	Other Non-Malignant Neoplasms															
Superficial x-ray	–	21	–	15	–	46	–	10	–	14	–	–	–	8	–	114
Deep x-ray	–	5	–	–	–	–	–	–	–	–	–	–	–	26	–	31
Cobalt[60]	13	105	10	85	–	48	–	170	–	23	–	46	–	87	23	564
Cesium[137]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Betatron	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Linear accelerator	–	58	–	48	38	316	–	193	–	20	10	90	–	–	48	725
Intracavitary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Interstitial	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Moulds and applicators	–	–	–	–	18	–	–	–	–	–	–	–	–	–	18	–
Systemic isotopes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Others*	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	1
SUB-TOTAL	13	189	10	149	56	410	–	373	–	57	10	136	–	121	89	1,435
TOTAL OF ALL TREATMENTS	2,320	25,224	2,092	10,571	6,341	27,681	4,212	28,962	1,143	5,401	3,156	20,392	1,581	10,138	20,845	128,369

* Others include radiation codes unknown.

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The distribution of these clinics reflects the general zones of service of the Foundation's Regional Cancer Centres in Hamilton, Kingston, London, Ottawa, Thunder Bay and Windsor; and of the Princess Margaret Hospital, Toronto.

HAMILTON	
Brantford	St. Joseph's Hospital
Burlington	Joseph Brant Memorial Hospital
Cambridge (Galt)	Cambridge Memorial Hospital
Guelph	Guelph General Hospital
Hamilton	McMaster Medical Centre and St. Joseph's Hospital
Niagara Falls	Greater Niagara General Hospital
St. Catharines	Hotel Dieu Hospital
Welland	Welland County General Hospital
KINGSTON	
Trenton	Trenton Memorial Hospital
LONDON	
Chatham	Public General Hospital
Kitchener	Kitchener-Waterloo Hospital
London	St. Joseph's Health Centre
Owen Sound	General and Marine Hospital
Sarnia	St. Joseph's Hospital and Sarnia General Hospital
St. Thomas	St. Thomas-Elgin Hospital
Stratford	Stratford General Hospital
Wingham	Wingham and District Hospital
Woodstock	Woodstock General Hospital
OTTAWA	
Cornwall	Cornwall General Hospital and Hotel Dieu Hospital
Ottawa	Riverside Hospital and Montfort Hospital
Pembroke	Pembroke Civic Hospital
THUNDER BAY	
Dryden	Dryden District General Hospital
Fort Francis	Fort Frances Clinic
Geraldton	Geraldton District Hospital
Sioux Lookout	Sioux Lookout General Hospital

TORONTO	
North Bay	North Bay Civic Hospital
Peterborough	St. Joseph's Hospital
Sault Ste. Marie	Plummer Memorial Public Hospital
Sudbury	Laurentian Hospital
Timmins	St. Mary's Hospital
WINDSOR	
Leamington	Leamington District Memorial Hospital

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THE ONTARIO CANCER INSTITUTE

THE ONTARIO CANCER INSTITUTE

incorporating

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August 5, 1987, was a milestone in the history of the Ontario Cancer Institute incorporating the Princess Margaret Hospital. The Minister of Health announced the site for the new OCI/PMH and planning could finally begin to meet the oncology needs of Ontario citizens.

The site supported by the Minister of Health was also the one preferred by the OCI/PMH -- the Ontario Hydro land on University Avenue adjacent to Mount Sinai Hospital. The unique grouping of hospitals plus the adjacent University of Toronto will provide a supportive environment for all our programs in patient care, research and education.

However commitment to fund a new building brings with it a double challenge. There is the excitement of looking ahead and planning, but there is also the responsibility of continuing care and programs at the current site for a number of years.

Planning for the new hospital has been an intensive effort for all staff throughout the Fall of 1987. Discussions included the Ontario Cancer Treatment and Research Foundation and the teaching hospitals because of the impact on oncology services throughout Metro Toronto. We expect the functional program to be complete in early 1988, but construction will not be complete until the mid-1990s. In the interim, planning has begun with Mount Sinai Hospital to install four radiation therapy machines in the basement of that hospital. These machines will be ready to treat patients by the end of 1989 or early 1990 and will significantly improve our ability to cope with the increasing numbers of cancer patients. When the new hospital opens, this space and the machines will stay as part of the Department of Radiation Therapy of the rebuilt Princess Margaret

Hospital. They will be close physically to the new building and will be accessible through a short tunnel; consequently, this is a logical plan.

In the clinical division, service and clinical investigation have been maintained and further developed under difficult circumstances. Some increase in space has been developed for the Department of Radiation Therapy. This has allowed improved planning facilities, including space for an additional simulator, a new Co-60 machine, a new linear accelerator, and space will now be prepared for another linear accelerator. These developments have not provided an increase in therapy machines but have allowed replacement of some of the older equipment. Expansion of the daycare facility was completed by the end of 1987. This will allow many more patients to be treated with chemotherapy as outpatients and will provide an excellent supportive environment for them during their treatment.

During the year, Dr. Helen Bean retired from the Department of Radiation Oncology but Drs. A. Fyles and S. Wong joined the department. Dr. Gunes Ege retired as Chief of Nuclear Medicine. Dr. Shelley Fine left the Department of Medicine to enter private practice, but still attends one clinic a week at the PMH. Drs. J. Mayo and P. Poon left the Department of Diagnostic Radiology, but Drs. R. Peto and S. Goshko were welcome additions to its staff. The new magnetic resonance imager was close to being commissioned by the end of the year. This powerful imager will make a significant contribution to patient diagnosis, to clinical and fundamental research programs, and will assist other hospitals in the community to improve this service to patients.

A major problem affecting all radiation therapy facilities in Canada is the continuing shortage of skilled therapy radiographers. Recruitment in the U.K. has provided some relief but the longterm solution is to expand the training programs here in Canada. The PMH School of Radiotherapeutic Technology is the largest of its kind in Canada. With approval from the Ministry, 50 students, double the previous number, will now be accepted from across Canada for the classroom portion of the 32-month program. Most radiation therapy centres will also increase the number of students they accept for the clinical part of their training. At OCI/PMH the number of first-year clinical positions will increase from 8 to 12 and full-time instructors will complement the extensive teaching done by the OCI/PMH staff.

Early in the coming year, the PMH will register its 200,000th patient, celebrate the 30th anniversary of its opening, and launch a fundraising campaign for the future. It will be a unique opportunity for all of us to reflect on the achievements of the past 30 years as we look ahead and plan for the next 30 years and beyond.

1987 was a year of research consolidation and advance. In biological research, staffing was completed as Drs. Norman Iscove and Christopher Paige took their appointments and organized their laboratories. Early in the year, the Biological Research Division received notification of its successful competition from a three-year grant from the NCIC. This success, following a similar happy

outcome for the Physics Division in the previous year, allowed scientists in both groups to proceed rapidly with their research programs. Each of the investigators in the Physics and Biological Research Divisions has triumphs to describe. In general, the research continues to apply the most recent experimental technology to the whole spectrum of the cancer problem.

R.S. Bush, M.D.
Director

TABLE I*

Number of Treatments Given in the PMH Department of Radiotherapy April 1985 – March 1987

EXTERNAL BEAM	1986-1987	1985-1986
Superficial x-ray	1,145	1,415
Deep x-ray	2,061	2,764
Cobalt	41,634	44,149
Linear accelerators:		
Low energy	8,652	9,374
High energy	28,567**	25,831***
Betatron†	–	1,933
TOTAL	82,059	85,466
Inpatient treatments	14,450	14,909
Outpatient treatments	67,609	70,557
TOTAL	82,059	85,466
SEALED SOURCES		
Intracavitary	247	243
Interstitial (needles, wires and seeds)	30	31
Strontium applicators	65	119
TOTAL	342	393

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1986-1987.

**Includes 3,154 treatments given at the Toronto-Bayview Regional Cancer Centre during April-August 1986.

***Includes 5,066 treatments given at the Toronto-Bayview Regional Cancer Centre since July 1985 to March 1986.

†Betatron was removed from service July 1985.

TABLE II*

Services Provided by PMH at Peripheral Clinics
April 1986 — March 1987

CLINIC	NEW PATIENTS SEEN		PERIPHERAL CLINIC VISITS**	
	Malignant	Other	Malignant	Other
North Bay	165	12	1,433	59
Owen Sound	31	—	669	15
Peterborough	15	—	1,801	30
Sault Ste. Marie	31	—	652	7
Sudbury	20	—	1,074	12
Timmins	51	11	1,001	42
TOTAL	313	23	6,630	165

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1986-1987.

**Including the visits when patients are first seen at peripheral clinics as well as subsequent visits for new and old patients.

TABLE III*

Cases of Malignant Disease
Distribution by Site of Malignancy and by Sex
April 1986 to March 1987

SITE	MALE	FEMALE	TOTAL
Head and neck	158	65	223
Ear, nose, throat	274	82	356
Gastrointestinal	407	282	689
Respiratory	678	316	994
Skin	369	277	646
Breast	9	1,258	1,267
Gynecological	—	686	686
Genitourinary	569	66	635
Lymphatic, hematopoietic	359	296	655
Other	304	248	552
TOTAL	3,127	3,576	6,703

*Data generated, with permission, from the Ontario Cancer Institute's Annual Report for 1986-1987.

TABLE IV*

New Patients with Malignant Disease
Distribution by Age and Sex
April 1986 to March 1987

SEX	0-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+	TOTAL
Male	36	111	167	267	610	881	651	183	17	2,923
Female	25	89	297	521	723	873	590	170	28	3,316
TOTAL	61	200	464	788	1,333	1,754	1,241	353	45	6,239

*Data generated, with permission, from the Ontario Cancer Institute's Annual Report for 1986-1987.

SPECIAL SERVICES

PROVISION OF SPECIAL DRUGS TO TREAT MALIGNANT DISEASE

The Foundation provides special chemotherapeutic agents to cancer patients who are residents of Ontario and are at home under the care of their doctors. This program was undertaken to assist those patients who find the cost of prolonged therapy with expensive drugs beyond their financial resources.

Drugs can be supplied only if attending doctors complete special prescription forms which are available from the Head Office, any of the Regional Cancer Centres, or the Princess Margaret Hospital. The completed form is mailed to the nearest Foundation centre or the Princess Margaret Hospital and the medication is mailed to the patient. The list of medications provided through the Foundation is available on request.

The total cost of the drug service in 1986 was $760,011.54 – an increase of 14.7% from the $662,563.20 in the previous year (Table I). In 1986, 10,710 prescriptions were filled and the cost per prescription has increased to $70.96 from $70.36 in 1985.

TABLE I

Cost of Drug Service
1977-1986

Year	Payments for Drugs	Total Cost of Drug Service
1977	148,418.40	152,021.06
1978	209,817.12	210,836.18
1979	257,136.92	261,512.36
1980	259,973.32	265,059.36
1981	307,376.30	307,676.97
1982	370,388.28	375,971.20
1983	448,401.93	450,872.94
1984	569,966.52	572,300.25
1985	658,111.38	662,563.20
1986	756,114.56	760,011.54

CARCINOEMBRYONIC ANTIGEN (CEA) AND STEROID-RECEPTOR ASSAYS PROGRAM

The Ontario Cancer Treatment and Research Foundation is administering and monitoring a program for carcinoembryonic antigen (CEA) and steroid-receptor assays which is funded by the Ministry of Health. The CEA assays for confirmed cases of cancer and the steroid-receptor assays for confirmed cases of breast carcinoma are available, at no charge, to a patient when these assays are performed in the designated laboratories listed below.

Current scientific literature indicates that CEA determinations are useful primarily in patients with cancers arising from the large bowel, breast, or lung. The analytical materials available at present have little utility for tumors of other organs. The only exceptions are cancer of the cervix and medullary cancers of the thyroid.

During the fiscal period April 1, 1986 to March 31, 1987, 4,677 steroid-receptor assays and 45,942 CEA assays have been performed in the designated laboratories.

All laboratories in Ontario are familiar with the program and can provide the details of the data required, sample requirements and specimen transportation. Specimens can be referred to the participating laboratories listed below either directly or through the laboratory which usually provides such services.

Laboratories in the CEA-Assay Program

McMaster University Medical Centre — Dr. E.D. Ryan
1200 Main Street West
Hamilton, Ontario L8S 4J9 tel: (416) 521-2100 ext. 6293

Kingston General Hospital — Dr. A.F. Clark
Stuart Street
Kingston, Ontario K7L 2V7 tel: (613) 548-3232 ext. 4185

Victoria Hospital — Dr. E.R. Tustanoff
375 South Street
London, Ontario N6A 4G5 tel: (519) 432-5241

Ottawa Civic Hospital — Dr. C. Lapkoff
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9 tel: (613) 725-4431

General Hospital of Port Arthur — Dr. N. Escott
460 North Court Street
Thunder Bay, Ontario P7A 4X6 tel: (807) 343-6707

Sunnybrook Medical Centre — Dr. A. Malkin
2075 Bayview Avenue
Toronto, Ontario M4N 3M5 tel: (416) 480-4648

Laboratories in the Steroid-Receptor-Assay Program

McMaster University Medical Centre — Dr. E.D. Ryan
1200 Main Street West
Hamilton, Ontario L8S 4J9 tel: (416) 521-2100 ext. 6293

Victoria Hospital — Dr. E.R. Tustanoff
375 South Street
London, Ontario N6A 4G5 tel: (519) 432-5241

Ottawa Civic Hospital — Dr. T. Ooi
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9 tel: (613) 725-4420

Sunnybrook Medical Centre — Dr. D.J.A. Sutherland
2075 Bayview Avenue
Toronto, Ontario M4N 3M5 tel: (416) 487-2722

University of Toronto — Dr. G.E. Mobbs
Medical Sciences Bldg., Rm. 7336
Toronto, Ontario M5S 1A8 tel: (416) 978-3553

DIAGNOSTIC BIOPSY SERVICE AND VOLUNTARY REPORTING BY PATHOLOGISTS

The diagnostic biopsy service was established by the Foundation to pay for biopsies on uninsured patients. In 1986, 6313 specimens were submitted by dentists (6290 in 1985).

The number of reports voluntarily submitted by the directors of pathology departments has continued to increase and, in 1986, 65,000 reports were submitted, a 3% increase over the 63,000 reports submitted in 1985.

These reports are used in the generation of cancer incidence data for Ontario and are most valuable in confirming the diagnosis of new cases. The Cancer Act, R.S.O. 1980, Chapter 57, Section 4, Item 7, provides protection for physicians, dentists and hospitals reporting information on cancer incidence to the Foundation. The information from the reports is used for epidemiological and statistical purposes only.

The Foundation gratefully acknowledges the continuing co-operation of the participating pathologists and hospitals, and the support of the Ontario Association of Pathologists in the acquisition of these data.

LODGES FOR AMBULATORY CANCER PATIENTS

At present, the Foundation funds and administers seven lodges for out-of-town ambulatory cancer patients attending the regional cancer centres for diagnosis and treatment. These lodges provide comfortable, supportive accommodation, with minimal supervision, at no cost to the patient. When beds are available, escorts are accommodated at minimal cost.

The Foundation provides this accommodation because the patient often has to travel a considerable distance to reach treatment centres. Without these facilities, the patient would be admitted to hospital at far greater expense to the Province.

Shown below is a list of current facilities and number of beds:

		Number of Beds
HAMILTON	Lakeview Lodge	20
KINGSTON	Quinte-Thousand Islands Lodge	33
LONDON	Thameswood Lodge	50
OTTAWA	Maurice J. Grimes Lodge	38
	Pavillon Alta Vista Lodge	30
THUNDER BAY	Amethyst House Lodge	18
TORONTO	Princess Margaret Hospital Lodge	105

Patients who require hostel accommodation while being treated at the Toronto-Bayview Regional Cancer Centre are housed in hostel facilities offered by Sunnybrook Medical Centre.

Expansion of the Maurice J. Grimes Lodge in Ottawa to a total of 60 beds is now underway and is expected to be completed by August 1988. Also, on September 10, 1987, the Pavillon Alta Vista Lodge was officially opened in Ottawa. This new facility, with 30 beds in total, will provide hostel accommodation to patients attending the General Division of the Ottawa Centre.

TRANSPORTATION OF CANCER PATIENTS

The Foundation covers the cost of transportation to any one of its regional cancer centres or to the Princess Margaret Hospital of those patients who live more than 25 miles from the centre and are considered to be in financial need. For patients 18 years or less, transportation is provided to the principal pediatric oncology treatment centres in the five health science complexes, namely:

HAMILTON	McMaster Medical Centre
KINGSTON	Kingston General and Hotel Dieu Hospitals
LONDON	War Memorial Children's Hospital, Victoria Hospital Corporation
OTTAWA	Children's Hospital of Eastern Ontario
TORONTO	Hospital for Sick Children

Usually transportation is arranged by the local unit of the Canadian Cancer Society, which subsequently is reimbursed by the Foundation.

For the fiscal year ended March 31, 1987, the total cost for transportation of patients was $695,730, compared to $799,209 for the fiscal year ended March 31, 1986.

CANCER INFORMATION SERVICE

In 1987, the Cancer Information Service began its first year as a province-wide program. The Service is funded jointly by the Ontario Cancer Treatment and Research Foundation and the Canadian Cancer Society Ontario Division.

The Service continues to provide the most up-to-date factual information on cancer and cancer-related resources. Use of the Physician Data Query (PDQ) computerized database developed by the National Cancer Institute continues to increase.

The Service continues to be well received with usage increasing gradually as the province becomes aware of it.

In the two years of the pilot project, over 6000 calls were received. Patients, family members and friends constitute the largest percentage of callers: 15-20% of inquiries are from patients, and 30-40% from family members and friends. Females continue to outnumber male callers 4 to 1. One of our major concerns is that most callers (over 65%) have a high school education or better. In the coming year, we hope to develop strategies to reach the population with lower levels of education.

Our users surveys continue to indicate that respondents are well satisfied with the service.

In the fall of 1987, the staff was expanded to include a health educator who will assist in the further development of the education and research components of the program.

Calls are answered Monday to Friday, between the hours 9:00 and 17:00.

RESEARCH PROGRAMS

SUMMARY OF OCTRF RESEARCH

PRESENT PROGRAMS

Career Scientists, Research Associates and Research Scholars

During 1987, the Foundation provided salary support, and, for new career scientists, start-up funds for equipment and supplies, for 12 career scientists: Drs. W.P. Jeeves and G. Singh in Hamilton; Drs. S.P.C. Cole, J.H. Gerlach and J.C. Kennedy in Kingston; Drs. A. Chambers, J. Harris, W.R. Inch, and J. Koropatnick in London; and Drs. H.C. Birnboim, R.G. Hawley and R.G. Liteplo in Ottawa; 5 research associates at the University of Toronto: Drs. M.A. Baker, J.G. Connolly, B.L. Gallie, H.F. Haberman, and G.E. Mobbs; and 2 research scholars: Dr. G.L. Hammond in London and Dr. J.C. Kudlow at the University of Toronto. To the OCTRF Regional Cancer Centres in Hamilton, Kingston, London and Ottawa, the Foundation also provided core grants to cover such items as secretarial support and travel costs for their career scientists.

Two new career scientists were appointed in 1987 – Dr. J.H. Gerlach in Kingston and Dr. R.G. Hawley in Ottawa. Dr. W.P. Jeeves of the Hamilton Centre resigned his position as career scientist to enter medical school. As a result of site reviews of Drs. M.A. Baker, B.L. Gallie, J.C. Kennedy and G.E. Mobbs during 1987, continuation of support was recommended in each case.

Senior Scientific Staff at the Ontario Cancer Institute

In addition to its funding of career scientists, research associates and scholars, the Foundation provides salary and core support for the senior scientific staff at the Ontario Cancer Institute. The annual research report of the Ontario Cancer Institute describes the projects carried out by these scientists.

The Division of Epidemiology and Statistics

The Foundation also supports members of the Foundation's Division of Epidemiology and Statistics in their research projects. Members of the Division, which has been affiliated with the Department of Preventive Medicine and Biostatistics at the University of Toronto since 1978, compete for operating funds through the various external granting agencies. In addition to their individual research pursuits, they assist research workers throughout the Province by providing epidemiological and biostatistical information, they respond to requests from the Ministry of Health on relevant issues, and they provide information to the scientific community and general public.

The Ontario Clinical Oncology Group (OCOG)

Since its inception in 1983, the OCOG has linked all OCTRF Regional Cancer Centres and the Ontario Cancer Institute. Studies have been organized in breast, lung and endometrial cancer.

In Stage I breast cancer – small primary tumor in the breast and pathologically negative axillary nodes – conservative therapy (Lumpectomy) alone is being compared to lumpectomy followed by adjuvant radiotherapy to the affected breast. This trial was initiated in the spring of 1984 and, by November 30, 1987, 615 patients had been entered from the Princess Margaret Hospital in Toronto and from the OCTRF Regional Cancer Centres in Hamilton, London, Ottawa, Thunder Bay and Windsor. Accrual of 800 patients should be complete by the fall of 1988.

Stage II breast cancer – primary tumor removed from the breast and some axillary nodes positive for metastatic disease but with no evidence of systemic cancer – is being studied in the postoperative period by comparing a three-month intensive adjuvant chemohormonal program with a nine-month less-intensive adjuvant protocol. This study also was initiated in the spring of 1984 and closed in the spring of 1987. At that time, over 400 patients had been entered in the two arms from the participating OCTRF Regional Cancer Centres in Hamilton, London, Thunder Bay and Windsor. The results of this second trial should be published shortly.

The chemoprophylaxis of lung cancer is being studied. In a randomized, double-blind study, etretinate – a vitamin A derivative – is administered to long-term cigarette smokers in an attempt to reverse the metaplasia detected in sputum. Recruitment of volunteers began in the fall of 1986 and 75 subjects are under study. The total sample size will be 120.

In endometrial carcinoma (high-risk local disease), a four-arm comparison has been mounted of standard versus wide-field radiotherapy, and medroxy-progesterone versus placebo. Most Ontario centres have expressed interest in this study and it will be activated as soon as a placebo is available.

In May 1987, the third annual three-day workshop on clinical investigation was held at McMaster University in the Department of Clinical Epidemiology and Biostatistics. The 21 participants came from the OCTRF Regional Cancer Centres, the Ontario Cancer Institute, and two Ontario medical schools. Several research ideas put forward by the three tutorial groups were discussed in some detail at a final plenary session. The participants enjoyed this excellent educational experience and the executive staff following up some of the ideas with these potential new investigators.

FUTURE POLICY

During 1987, Dr. J.C. Laidlaw, Director of Research and Education, visited all OCTRF Regional Cancer Centres, and from these visits and extensive discussion at meetings of the OCTRF Research Advisory Panel the following principles or guidelines were developed for research at the Centres. These principles have been approved by the Centre directors and by the Board of the Foundation.

Research Milieu

- The OCTRF-funded investigators cannot of themselves form a critical mass. To bring this about, they and colleagues from the nearby university hospital and/or university must form a larger group.
- The critical mass of investigators thus formed should be in geographical contiguity.
- For the most part, the investigators should be organized in groups –each with its own theme.
- Wherever possible, the groups of investigators should provide a continuum of research from bench to bedside to community. This process could be enhanced by the presence of clinician scientists whose disciplines could extend from molecular genetics to clinical epidemiology to behavioural science.
- The principle of "excellence through heterogeneity" should be followed. This means that the OCTRF Regional Cancer Centres are free to develop their own programs, areas of concentration, and collaborations.

Research Leadership

For the cancer research group itself and for the larger critical mass of investigators of which they would form a part, great efforts should be made to ensure intellectual leadership, which provides effective administration and facilitation of research, and stimulates communication and collaboration across the continuum of health research from bench to bedside to the community.

Excellent Investigators

It goes without saying that the Foundation must select investigators whose research training and performance are of high quality.

Consortial Funding

It is clear that to achieve the research milieu described, funding will be needed not only from the OCTRF but also from university hospitals, universities and, for operating support at least, from agencies such as the National Cancer Institute of Canada, and the Medical Research Council of Canada.

In an attempt to apply these principles, Drs. L. Siminovitch, (Chairman, OCTRF Reseach Advisory Panel), J.W. Meakin and J.C. Laidlaw have met with the Deans of Medicine, Chief Executive Officers, Board members and staff of the appropriate university hospitals, and members of the university staff, in Hamilton, Kingston, London, Ottawa and Toronto (Sunnybrook Hospital - Toronto-Bayview Regional Cancer Centre).

In all of these centres considerable progress has been made in developing a critical mass of research workers, research leadership and milieu, and consortial funding. In this effort, the Chairman of the OCTRF Board, Mr. Michael Meighen, has been of great help.

The Directors of the OCTRF Regional Cancer Centres in Thunder Bay and Windsor, and the Northeastern Ontario Oncology Program in Sudbury, have been exploring with their local universities and with the Director of Research and Education means by which research activity might be enhanced at their Centres.

The OCTRF Research Advisory Panel has been discussing the initiation of a program for support of clinician scientists who would spend the majority of their time in research. Dr. Barbara Campling in Kingston and Dr. Diane Logan in Ottawa are the forerunners of such a program. Also the Panel has been exploring means of enhancing at the Centres the research activities of clinicians who have had peer-reviewed funding and publications but who, because of service and administrative commitments, have beeen able to spend only a small portion of their time in research.

PROPOSAL FOR A CANCER PREVENTION RESEARCH GROUP OF ONTARIO

This proposal arose out of the recommendations of the Standing Committee on Procedural Affairs of the Legislative Assembly of Ontario (1983), the Provincial Role Study of Cancer Services in Ontario (1985), and the Ad Hoc Cancer Research Advisory Committee of the Foundation (1985). All emphasized the need for more research and education with respect to the primary prevention of cancer in Ontario.

The proposal developed by Dr. J.E. Till and the Research Advisory Panel, does not ask for support for any specific project; instead, it describes a framework within which such projects could be developed and implemented. The emphasis is on interventions, that is, on actions designed to prevent cancer, rather than on studies of the etiology of cancer.

The proposed framework has two main components: a core group at one selected location; and a network to make effective use of the available talent at other locations. Probably the core group would consist of approximately three senior scientists and their supporting staff, and ideally would be multidisciplinary. The members of the core group and of the network would have access to peer-reviewed support, including that for pilot projects, trainees, workshops and

travel. Beyond the pilot stage, we would seek operating funds for projects from provincial or national granting agencies.

The group would be established on the basis of a competition, beginning with a request for proposals; this request would set out the information to be included in a proposal, such as the research theme, the structure to be used in the development of the core group and the network, a budget, and an outline of proposed initial projects. The successful group would be expected to compete for core group re-establishment at 10-year intervals. Between these intervals, peer review, involving on-site visits, would monitor the uses being made of the infrastructure support for the core group and the network.

The Canadian Cancer Society and the National Cancer Institute of Canada have indicated an interest in these objectives. The proposal, which has been submitted to the Ontario Ministry of Health, is being examined in relation to other recommendations about ways to foster efforts to prevent this disease.

J.C. Laidlaw, M D
Director of Research and Education

RESEARCH PERSONNEL SUPPORTED BY OCTRF

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G. Singh, Ph.D.

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University of Toronto:
J.E. Kudlow

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Hamilton Regional Cancer Centre

DAMAGE INDUCED BY LIPOPHILIC CATIONIC COMPOUNDS ON OXIDATIVE PHOSPHORYLATION*

G. SINGH**, *Hamilton, Ontario*

Rhodamine-123 and safranine are fluorescent lipophilic cations which accumulate in energized mitochondria. It has been demonstrated that rhodamine-123 has selective anticarcinoma activity both in epithelial-derived tumor cells and in tumor-injected mice. To understand the molecular basis of the antitumor activity displayed by rhodamine-123, we investigated the bioenergetic functions of mitochondria incubated with the lipophilic compound.

Rhodamine-123 and safranine inhibit the stimulation of mitochondrial respiration by ADP in a similar concentration range. This inhibition occurs whether the mitochondria are respiring on succinate as a substrate or ascorbate plus tetramethylphenylene diamine. Adenosine triphosphate hydrolysis was stimulated twofold by high lipophilic cationic concentrations. These results demonstrate that rhodamine-123 and safranine affect oxidative phosphorylation in a similar fashion.

This work suggests that inhibition of the adenosine nucleotide translocase and possibly complex IV are possible sites of damage induced by lipophilic cationic compounds.

This project is supported by a grant from the Medical Research Council of Canada.

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*CS-106-2

**Career Scientist, OCTRF Hamilton Regional Cancer Centre; and Assistant Professor of Pathology, McMaster University, Hamilton

MITOCHONDRIAL PHOTOSENSITIZATION BY PHOTOFRIN II*

G. SINGH**, W.P. JEEVES† and B.C. WILSON‡
Hamilton, Ontario

We treated V-79 Chinese hamster cells grown as monolayers or as multicell spheroids with photofrin II (10 ug/ml for 16 hr) and various doses of red light irradiation, and studied the resulting biochemical and functional damage to cell mitochondria. Biochemical damage was measured by a decrease in the activity of two enzymes – succinic dehydrogenase and cytochrome-C oxidase. Mitochondrial function was monitored by respiration and by the ability of mitochondria to concentrate rhodamine-123 via their electrochemical gradient.

The activities of both succinic dehydrogenase and cytochrome-C oxidase were found to decrease in a light-irradiation, dose-dependent manner. The respiratory control quotient decreased in parallel with a decrease in the activities of the respiratory chain proteins. Our data also show a distinct temporal difference in the relative progression of mitochondrial damage and cell death as assessed by loss of discrete rhodamine-123 localization and trypan-blue or ethidium-bromide infiltration, respectively. Mitochondrial damage was detected immediately, as seen by delocalization of rhodamine-123 resulting from dissipation of the electrochemical gradient in damaged mitochondria. Trypan-blue infiltration occurs with a distinct time lag, although at the highest light exposures tested, the times at which mitochondrial damage and cell death are observed appear to converge.

The findings are consistent with the hypothesis that, at least for long DHE incubation times, the mitochondrion is a primary target of photofrin II photosensitization. The subsequent changes in cell membrane permeability may be a delayed result of decreased bioenergetics of the photofrin II photosensitized cell.

This project is supported by the Medical Research Council of Canada and the National Cancer Institute of Canada.

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*CS-106-3

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† Career Scientist, OCTRF Hamilton Regional Cancer Centre
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Kingston Regional Cancer Centre

PHOTOCHEMOTHERAPY: CHEMICAL AND BIOLOGICAL CORRELATIONS*

J.C. KENNEDY** and R.H. POTTIER†, *Kingston, Ontario*

Typically the pH of the interstitial fluid in malignant tissues is 0.3 to 0.5 of a pH unit below that of normal tissues. Such a difference in pH can result in significant differences in the state of ionization of drugs that are either weak acids or weak bases. Usually ionizable drugs are most soluble in plasma membrane lipids when in the non-ionized state. In the past year, most of our research has been directed toward testing our working hypothesis: that cells in malignant tissues will accumulate ionizable photochemotherapeutic agents preferentially if their pk_as are such that non-ionized drug molecules occur at maximum concentration at pH values slightly lower than 7.2 to 7.4 -- the pH range that characterizes the interstitial fluid of most normal tissues. Our initial model was hematoporphyrin IX (HpIX), a tumor-localizing drug that is both a weak acid and a weak base. According to our working hypothesis, HpIX should be non-ionized maximally at a pH somewhat lower than 7.2 -- the usual lower limit of the range of pH values found in normal tissues. By combining results obtained from six different techniques of physical chemistry – volumetric titration, octanol/water partition, optical transmittance spectroscopy, photoacoustic spectroscopy, fluorescence emission spectroscopy, and fluorescence excitation spectroscopy – we determined the pk_as for protonation of the two imino nitrogens and for ionization of the two carboxylic acid groups of HpIX. As predicted from our hypothesis, the pH (6.3) at which the non-ionized form of HpIX was present at maximum concentration was definitely lower than the lowest value ordinarily observed in normal tissues. Studies to determine the effect of pH upon the concentration of the various ionic species of other ionizable tumor-localizing drugs are now in progress.

This project is supported by a grant from the Medical Research Council of Canada.

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*CS-101-1

**Career Scientist, OCTRF Kinston Regional Cancer Centre; and Associate Professor of Oncology and of Pathology, Queen's University, Kingston

† Professor of Chemistry and of Chemical Engineering, Royal Military College, Kingston; and Associate Professor of Urology, Queen's University

MULTIDRUG RESISTANCE IN HUMAN LUNG TUMORS*

S.P.C. COLE**, *Kingston, Ontario*

The development of resistance to antineoplastic agents is a major problem in the practice of clinical oncology. We have isolated a multidrug resistant (MDR) variant, designated H69AR, of the human small-cell lung cancer (SCLC) cell line, NCI-H69, as a model of the clinical problem of MDR in SCLC. In contrast to many previously described MDR cell lines, H69AR does not have enhanced P-glycoprotein at the DNA, RNA or protein level. The net accumulation of Adriamycin in H69AR cells is less than in its drug-sensitive parent, although Adriamycin efflux appears similar for both lines. We have produced a panel of murine monoclonal antibodies (MAbs) specific for H69AR cells in order to study the molecules associated with MDR in our system. Indirect immunofluorescent staining of unfixed and 70% methanol-fixed cells and FACS analysis suggest that MAb 2.54 reacts with a cell-surface epitope while MAbs 2.181, 3.50, 3.80, 3.177, 3.186 and 3.187 react with internal epitope(s). None of the MAbs crossreact with the P-glycoprotein-containing MDR line $CH^{2R}C5$, and only MAb 2.54 crossreacts with the MDR human ovarian cell line -- A2780 AD645. In contrast, eight of the MAbs crossreact specifically with HT1080/DR4 -- another MDR human tumor cell line which shows no evidence of enhanced P-glycoprotein expression. These MAbs may be useful in the investigation of the resistance mechanism in non-P-glycoprotein-mediated MDR and in detection of MDR cells in SCLC patients.

This project is supported by grants from the Medical Research Council of Canada, the National Cancer Institute of Canada, the Ontario Thoracic Society, the Cancer Research Society, and the Clare Nelson Bequest of the Kingston General Hospital.

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*CS-107-1

**Career Scientist, OCTRF Kingston Regional Cancer Centre; and Assistant Professor of Oncology, and of Microbiology and Immunology, Queen's University, Kingston

MULTIDRUG RESISTANCE: MOLECULAR INTERACTIONS*

J.H. GERLACH**, *Kingston, Ontario*

I am establishing a molecular biology laboratory to investigate the role of P-glycoprotein and other plasma membrane components in multidrug resistance in mammalian cells. The development of such resistance continues to be a major limiting factor in combination chemotherapy with curative intent. In tissue-culture models of multidrug resistance, the most consistent finding is the overexpression of P-glycoprotein – a 170 kDa plasma membrane protein. This molecule functions as a drug "export pump" and is thought to use adenosine triphosphate to actively transport a wide variety of chemotherapeutic agents from resistant cells. The overexpression of P-glycoprotein in human ovarian ascites and human sarcoma samples strongly suggests that the multidrug resistance phenomenon will be of clinical importance in at least some human malignancies.

I will generate variants with alterations in net drug accumulation to identify gene products which interact with P-glycoprotein in the plasma membrane. Recombinant DNA techniques will be used to clone these genes and the deduced amino acid sequences will then be analyzed. The primary goal of this research is to better understand the molecular basis of drug translocation and thus find targets for increasing the efficacy of combination chemotherapy.

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*CS-109

**Career Scientist, OCTRF Kingston Regional Cancer Centre; and Assistant Professor of Oncology and of Biochemistry, Queen's University, Kingston

London Regional Cancer Centre

USE OF MAGNETIC RESONANCE SPECTROSCOPY TO MONITOR CARDIOTOXICITY CAUSED BY ADRIAMYCIN*

W.R. INCH**, *London, Ontario*

The use of Adriamycin is limited by its cardiotoxic effect[1], which may be acute – occurring within minutes of its administration, or chronic – developing several weeks or months after treatment. The latter can be extremely debilitating and even cause death. Topical magnetic resonance spectroscopy (MRS) allows us to measure in intact tissues of a number of biochemical parameters which otherwise are only obtained by destructive tissue analysis. In Victoria Hospital, we have a spectrometer available that is capable of detecting proton (H-1), carbon (C-13) and phosphorus resonance (P-31). Since the phosphorus atom is associated with molecules involved in energy production, this noninvasive technique of MRS can be applied to studies of cardiac metabolism. Four animals have been used to develop the surgical procedure, spectrum collecting methods, positioning in the magnet, coil design and tuning. ^{31}P spectra were obtained every 3 weeks immediately before the injection of Adriamycin. Cardiac ejection fraction was measured using Sn++ and Tc-99m and the electrocardiogram was recorded at regular intervals. Histologic sections of the heart were examined at 2, 3 and 4 months using representative animals from each group.

Preliminary MRS measurements have been made on a number of cats and rabbits[2] and we believe the major technical problems have been overcome. After various probe configurations were investigated, one we found that gives a signal-to-noise ratio comparable, if not better, than the previously published spectra. The problem of cardiac motion has been addressed and both electrocardiogram and respiratory gating have been tried successfully.

Once the model is established, we plan to investigate the use of free radical scavengers as means of reducing cardiotoxicity. For example, butylated hydroxyanisole, given before Adriamycin, would be at a higher concentration in the heart than in a tumor, which usually has a poor blood supply. Therefore, a therapeutic gain might be achieved by using such a combination.

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*CS-100-1

**Career Scientist, OCTRF London Regional Cancer Centre; and Professor of Radiation Oncology and of Medical Biophysics, University of Western Ontario, London

METALLOTHIONEIN GENE AMPLIFICATION AND REGULATION IN VIVO*

J. KOROPATNICK**, *London, Ontario*

Metallothionein Gene Amplification

We have demonstrated specific in vivo amplification of the gene for mouse metallothionein-1 (MT-1) after exposure to cadmium – an inducer of expression of the gene[1]. We have explored this phenomenon to show that: a) initially extra copies of the MT-1 genes are inactive in expressing gene product, but become active three days after induction; and b) changes in nuclease sensitivity, which indicate an unusual altered chromatin structure, accompany the changes in the gene's transcriptional activity. The observed amplification appears to be part of a mechanism to regulate MT-1 expression in the mouse. In liver, only a subpopulation of highly differentiated hepatocytes – approximately 10% of the liver cell population – respond to induction by producing elevated levels of MT protein. Using fluorescence-assisted cell sorting, we have observed that only the diploid cell subpopulation in liver undergoes DNA replication in the first few hours following high level cadmium induction of MT-1 gene amplification. In view of this, we are exploring the possibility that apparent gene amplification may be due to selective DNA replication and eventual cell division within a subpopulation of mouse liver cells with constitutively amplified MT-1 genes, without invoking *de novo* amplification events. Understanding of this process would provide insight concerning the generation of cells with amplified genes and variable drug-resistance and metastatic potential which appear in tumor-cell populations in vivo.

Metallothionein and Radio- and Chemotherapy Resistance

Radiation and many chemotherapeutic agents act to kill tumor cells by formation of intermediate free radicals. Metallothionein protein has the capacity to bind many such free radicals and so decrease their ability to damage cells[2,3]. We have observed that Co^{60} irradiation or cisplatin treatment of mice results in tissue-specific induction of metallothionein mRNA. We are exploiting this observation to determine whether constitutive or inducible over-expression of metallothionein confers resistance to the effects of radio- or chemotherapy on tumor cells.

This project is supported by a grant from the Natural Sciences and Engineering Research Council of Canada.

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*CS-103

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USE OF THE IMMUNE-DEFICIENT EMBRYONIC CHICK TO STUDY TUMOR METASTASIS*

A.F. CHAMBERS**, *London, Ontario*

Metastasis is responsible for many failures in cancer treatment. One requires in vivo assays to study mechanisms of metastasis, and recent work on molecular and genetic aspects of metastasis has emphasized the need for assays in immune-deficient hosts. We have developed an assay for metastasis using a novel immune-deficient host -- the embryonic chick[1]. We are using it to examine the metastatic potential of oncogene-transformed cells, and also are continuing its characterization.

Previously we showed that NIH3T3 cells transformed by the *ras* oncogene are metastatic in the chick embryo assay, and will grow in embryonic organs following intravenous injection[2]. We are characterizing the heterogeneity of individual clones of *ras*-transformed NIH3T3 cells. Not all clones are metastatic, and metastatic ability depends in part, but not entirely, on levels of the *ras* gene product -- p21.

Also we are characterizing this assay further to better understand the fate of tumor cells in the circulation. Recently we have shown that the majority of individual B16 melanoma metastases that arise in chick liver following intravenous injection are clonal, i.e. arose from a single cell. This situation, which parallels that observed in assays in syngeneic mice, suggests that a mature immune system does not affect the clonality of metastasis. It should be noted that a significant minority of individual metastases in assays in both chick embryo and mouse are not clonal, and that the diversity seen in some metastases may reflect different phenotypes of progenitor cells, as well as heterogeneity arising during the growth of the metastatic tumor.

This project was supported by grants from the National Cancer Institute of Canada, and the Cancer Research Society, Inc.

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*CS-150-1

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SOMATIC CELL GENETIC ANALYSIS OF METASTATIC CELLS*

A.F. CHAMBERS** and J.F. HARRIS**, *London, Ontario*

The generation of heterogeneity is an important feature in the development of metastatic cells. We have proposed a dynamic heterogeneity model in which tumor cells acquire and lose certain metastatic properties[1,2]. We have used Luria-Delbruck fluctuation analyses of clonal populations of tumor cells to measure rates of generation of metastatic variants. We found that one mechanism for the maintenance of a more highly metastatic phenotype in B16 melanoma cells is through a higher rate of generation of metastatic variants[3]. We have extended these results to KHT fibrosarcoma cells[4].

In our study of tumor cell instability, we have taken a related approach -- that is to analyze the relationship between malignant transformation and instability for the generation of drug-resistant cells. We found that there was no obligatory relationship between these two phenotypes, using cells carrying a temperature-sensitive oncogene. These results, coupled with results from other goups, suggest that there are complex inter-relationships between malignant transformation and genetic and epigenetic instability and that we have much to learn about the generation of phenotypic instability in tumor cells.

This work was supported by a grant from the Medical Research Council of Canada.

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*CS-150-2

**Terry Fox (Ontario) Career Scientist, OCTRF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, and of Microbiology and Immunology, University of Western Ontario, London

EMBRYONAL CARCINOMA CELL MODEL OF EXPERIMENTAL METASTASIS*

J.F. HARRIS**, *London, Ontario*

Mouse embryonal-carcinoma (EC) cells provide an interesting model by which to investigate the basic biology of metastasis. When EC cells are injected into the tail vein of a mouse in an experimental metastasis assay, liver (rather than lung) colonies are formed, although the cells interact first with the lung capillary system. The liver colonization of EC cells differs from that observed in our previous studies using mouse fibrosarcoma[1] and melanoma[2] cells, which form experimental lung metastases almost exclusively.

We have proposed a dynamic heterogeneity model which proposes that specialized metastatic cells are generated rapidly during clonal expansion[1,2]. When parallel clones of EC cells were grown to a measured cell number and tested for metastatic ability, it was observed that the frequency of liver tumors increased with increasing clonal population size until an equilibrium was achieved. Mathematical analysis of the results indicates that the effective rate of generation of the liver metastasizing variant cells is $(7 \pm 3) \times 10^{-6}$ cell^{-1} generation^{-1}. Thus, in addition to its previous applications to lung metastases of fibrosarcoma and melanoma cells, the dynamic heterogeneity model can be applied to the description of liver metastases of EC cells.

Although the effective rate of generation of metastatic variant cells is defined by the cell-cloning experiments, the nature of the event(s) generating the metastatic cells is unknown. By inducing the differentiation of EC cells with retinoic acid for three days, the partially differentiated cells lose their ability to form liver colonies and acquire the ability to form lung colonies. Monoclonal antibodies have been raised to antigens modulating in response to retinoic acid treatment in an attempt to define the cell-surface antigens responsible for the change in organ specificity.

This project was supported by a grant from the National Cancer Institute of Canada.

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*CS-151

**Terry Fox (Ontario) Career Scientist, OCTRF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, and of Microbiology and Immunology, University of Western Ontario, London

STABILITY OF HUMAN MONOCLONAL ANTIBODY PRODUCTION IN MOUSE-HUMAN HYBRIDOMA CELLS*

J.F. HARRIS** and J. KOROPATNICK**, *London, Ontario*

The instability of human monoclonal antibody production by hybridoma cells limits the usefulness of this important technology. To understand the mechanism of loss of antibody production, we have described the quantitative analysis of the stability of human monoclonal antibody production by hybridomas. Selected clones derived from fusion between the SHM-D33 heteromyeloma line and human lymphocytes were found to be as stable (with respect to antibody production) as mouse hybridoma cells[1].

To define the mechanism of loss of antibody production, we analyzed independent stable and unstable hybridomas, and independently derived, antibody-negative segregants, using DNA probes. We employed an *Alu* consensus sequence probe (*Blur 8*), which hybridizes to human but not to mouse DNA, and human immunoglobulin (Ig) gene probes to detect human Ig genes. Results suggest that: 1) the relevant mechanism in loss of human antibody production is loss of Ig genes rather than transcriptional inactivation; 2) there is considerable heterogeneity in human DNA content in antibody-positive human hybridoma cells (the absolute amount of human DNA per cell is variable by more than 8-fold); and 3) segregation to antibody-negative status is accompanied by a dramatic increase (approximately 10-fold) in the rate of loss of human DNA, leading rapidly to loss of 95% or more of the human DNA in segregant hybridomas. Accelerated loss of human DNA rapidly would increase the possibility of losing structural human Ig gene sequences with consequent loss of antibody production. We are exploring the possibility that: a) heteromyeloma parent cells are heterogeneous for the ability to produce stable mouse-human hybridomas; and b) resulting hybridomas vary, between clones, in stability of human antibody production. We hypothesize that critical human or mouse genes, which promote stability in hybridomas, are lost or altered in expression during the events that lead to segregation. A better understanding of the factors promoting retension of human DNA and stability of antibody production will allow us to select clones of optimal stability for long-term culture and antibody production.

This project is supported by a grant from the Cancer Research Society, Inc.

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*CS-151-1

**Career Scientist, OCTRF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, and of Microbiology and Immunology, University of Western Ontario, London

STRUCTURE AND FUNCTION OF PLASMA STEROID BINDING PROTEINS*

G.L. HAMMOND**, *London, Ontario*

Human blood contains two important, high-affinity, plasma steroid binding proteins that are unrelated to the albumin gene family, and are generally known as corticosteroid binding globulin (CBG) and sex-hormone binding globulin (SHBG). Although steroid hormone transport undoubtedly is a major function of these proteins, they also appear to regulate the bioavailability of steroid hormones and may participate in the delivery of steroids to specific target cells[1].

It is also known that deficiencies in plasma levels of CBG are found frequently in patients with hematological malignancies[2], and abnormalities in plasma SHBG levels, and/or its steroid binding properties have been associated with breast and endometrial cancer in women[3,4]. Therefore, to define the structural and functional aspects of CBG and SHBG more precisely, we have used molecular biological techniques to clone and sequence cDNAs for these proteins, and have thereby deduced the primary structures of both proteins[5,6]. This work has revealed that CBG is a member of the serine protease inhibitor (SERPIN) gene family, and suggests that the structural relationship between CBG and the SERPINs may be of functional importance.

The availability of these cDNAs will permit the isolation and characterization of the SHBG and CBG genes in humans and experimental animal models, and thereby facilitate studies of the hormonal regulation of their expression. In addition, site-direct mutagenesis will be used to produce variant proteins, which should help identify the structural and functional properties of these proteins at the molecular level. It is anticipated that this work will help us understand more clearly the mechanisms by which steroid hormones enter target cells and provide new insight into the etiology of hormone-dependent cancers.

These projects are funded by the Medical Research Council of Canada and the Ontario Thoracic Society.

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*RS-230

**Research Scholar, OCTRF London Regional Cancer Centre; and Associate Professor of Obstetrics and Gynecology, University of Western Ontario, London

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ADDITIONAL INVESTIGATIONS

Dr. L. Levin, Director of the London Regional Cancer Centre, reports on the following clinical research investigations:

NUCLEAR MAGNETIC RESONANCE STUDIES

Dr. J. Skillings continues to evaluate the role of magnetic resonance (MR) in assessment of abdominal disease in patients with Hodgkin's disease. In conjunction with the Ottawa Centre, further studies of MR will be performed to assess lung injury from chemotherapy.

Drs. W.R. Inch and H. Peemoeller are using two-dimensional nuclear MR to monitor the relaxation parameters in normal, preneoplastic and neoplastic systems to further clarify the potential of nuclear MR in studies of cancer. This work is supported by a research grant from the University of Waterloo.

LYMPHOMAS

The lymphoma group continues to accrue patients in the NCIC-sponsored, Phase III study of escalated Bactrim/Septra in poor-prognosis, non-Hodgkin's disease. Dr. Skillings is study chairman for a new phased study of acivicin in relapsed, poor-prognosis lymphomas. Another study continues using menogarol with relapsed nodal lymphoma.

EXPERIMENTAL ONCOLOGY

Dr. J. Koropatnick, in colaboration with Dr. H. Ceri (Department of Biology, University of Calgary), is cloning gene sequences responsible for lectin proteins of higher eukaryotes, which may play a role in cellular transformation and metastasis.

Dr. W.R. Inch is studying the biology of hypoxic cells and the diffusion of cytotoxic drugs into multicell spheroids. This work is supported in part by Upjohn Co. in Michigan, and the Cancer Research Society, Inc.

BRAIN TUMOR STUDIES

Dr. J.G. Cairncross and his colleagues are participating in several clinical and basic research projects focused on the treatment of malignant glioma. In the laboratory they are studying the effects of culture conditions, differentiation-promoting agents, and extracellular matrix proteins on glial filament expression and the cell-surface antigenic profile of cultures human gliomas. Also, in collaboration with Dr. A. Chambers, he is studying the metastatic potential of human malignant gliomas.

The clinical research includes chemotherapeutic approaches to new and recurrent malignant gliomas; the effects of steroids and non-steroidal anti-inflammatory agents on the CT and MRI appearance of malignant gliomas; myelography and MRI scanning of the spine in patients with suspected spinal

epidural metastasis; cognitive function in successfully treated, train-tumor patients; response evaluation in patients with recurrent malignant glioma; chemotherapeutic approaches to primary cerebral lymphoma, etc. The clinical studies are done in collaboration with Drs. David Macdonald and Dwight Moulin and other members of our multidisciplinary neuro-oncology group.

Ottawa Regional Cancer Centre

MECHANISM OF OXYGEN-RADICAL DAMAGE TO CELLULAR DNA AND ITS ROLE IN TUMOR PROMOTION AND TUMOR PROGRESSION*

H.C. BIRNBOIM**, *Ottawa, Ontario*

For several years our laboratory has been studying the mechanism by which a "physiological" oxygen radical, superoxide anion (O_2^-), can cause strand breaks in DNA of human cells. This oxygen radical can be produced by a variety of phagocytic cells, such as neutrophils, present in inflammatory exudates and in solid tumors. One of the most potent stimulants of oxygen radical production by neutrophils is phorbol myristate acetate (PMA), an inflammatory and tumor-promoting agent. When human neutrophils are stimulated with PMA, O_2^- is released from the surface of the cells and soon afterwards strand breaks appear in their DNA. We have hypothesized that, within tumors, the oxygen-radical products of neutrophils induce strand breaks in the DNA of neighbouring tumor cells and that these breaks may lead to the activation of oncogenes.

Our current evidence indicates that metabolic steps (as opposed to purely free-radical reactions) are involved in the production of DNA strand breaks by O_2^-. It is postulated that the following series of events lead to strand breaks. O_2^- is released from the cell membrane into the extracellular environment following stimulation with PMA. The O_2^- reacts with a component of the cell membrane inducing a transmembrane signal. There follows a series of events including a protein phosphorylation and Ca^{++} and Mg^{++}-requiring steps. A nuclease-like activity is activated and DNA strand breaks are produced. Some of the evidence supporting this model is the following: No strand breaks occur if the O_2^- is scavenged by a specific enzyme, superoxide dismutase; anion channel blockers, which prevent O_2^- from entering the cell, have no effect on the level of breaks; sodium orthovanadate, a phosphoprotein phosphatase inhibitor, enhances the level of breaks; ionophore A23187 reduces the number of breaks in the absence of Ca^{++} and is more effective if Mg^{++} is also absent; and orthovanadate reverses the inhibition by A23187 only if Mg^{++} is present. Taken together, this evidence supports the notion that metabolic processes are triggered by the oxygen-radical, O_2^-, leading to strand breaks. This work may provide new insight into the relation between inflammatory processes and the development of malignancy.

This project is supported by a grant from the Medical Research Council of Canada.

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*CS-104-1

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STUDY OF SIGNAL TRANSDUCTION PROCESSES FOLLOWING ACTIVATION OF PROTEIN KINASE C RESPONSIBLE FOR THE INDUCTION OF C-FOS PROTO-ONCOGENE EXPRESSION*

H.C. BIRNBOIM** and R.G. LITEPLO†
Ottawa, Ontario

The c-fos proto-oncogene, which encodes a nuclear protein of unknown function, has been the subject of intense study in many laboratories because it is thought to play an important role in the control of cell growth and differentiation. There are numerous examples of quiescent cell types in which the c-fos gene is not expressed but it is readily and transiently turned on when the cells are stimulated to divide. We have been studying the control of c-fos expression in murine fibroblasts which are brought into a quiescent state either by growth to confluence or by serum starvation. When such cells are stimulated by treatment with phorbol myristate acetate (PMA) -- an activator of protein kinase C -- expression of the c-fos gene is induced within a few minutes and reaches a peak within 30 minutes. Relatively little is known about the sequence of events between stimulation of protein kinase C and activation of the gene in these cells. Phosphorylation of protein(s) is presumed to play an important role. Recently we found that indomethacin, a drug used at lower concentrations to inhibit the cyclo-oxygenase pathway of arachidonic acid metabolism, markedly and rapidly inhibits the induction of c-fos expression by PMA at higher concentrations. Under conditions where c-fos expression is inhibited, there is little or no effect on ATP levels and incorporation of ^{3}H-uridine into RNA. The inhibition by indomethacin is fully reversible up to at least one hour. The drug is cytostatic for logarithmically growing cells, i.e., it blocks cell growth and growth resumes when the drug is removed after 24 hr. Understanding the mechanism of action of this drug should provide information about the signal transduction processes involved in regulation of expression of this proto-oncogene.

This project is supported by grants from the Medical Research Council of Canada and the National Cancer Institute of Canada.

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*CS-104-2

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EVALUATION OF POLYAMINE AND AMINO ACID PROFILES IN SMALL-CELL LUNG CANCER UNDERGOING TREATMENT IN CLINICAL TRIALS*

W.K. EVANS**, F.A. SHEPHERD†, K.N. JEEJEEBHOY‡
H. ANDERSON*** and E. LI‡,
Ottawa and Toronto, Ontario

Polyamines are important in the regulation of protein, RNA and DNA synthesis and their biosynthesis is essential for cell proliferation. Elevations of polyamine levels have been observed in the urine, plasma and erythrocytes of patients with various malignancies including small-cell lung cancer. During a study of the role of total parental nutrition during cytotoxic therapy for small-cell lung cancer, we observed an abnormal amino-acid profile in untreated patients. At baseline, we noted low levels of methionine, ornithine and citrulline, and increased levels of glutamine, glutamic acid, asparagine, arginine and aspartic acid. Response to treatment led to an increase in methionine levels and decrease in glutamine and glutamic acid. These observations suggested to us that tumor-related polyamine synthesis might be responsible for the abnormal amino-acid profile. To prove this hypothesis, we undertook to measure plasma amino acids and polyamines before treatment, during treatment (at the time of tumor response or complete remission) and again when the tumor had progressed. Data collected to date support this hypothesis. The amino acid profile returned to normal with response to therapy and the polyamine levels also decreased. The study is continuing to accumulate the number of fully evaluable patients necessary for statistical analysis. These observations may have important implications for future studies of anticancer therapy and nutritional support. Such investigations might explore the impact of polyamine synthesis inhibitors on polyamine and amino acid levels in small-cell lung cancer patients with chemotherapy-resistant disease and the use of polyamine synthesis inhibitors in combination with chemotherapy. Previous studies of enteral and parenteral nutrition in cancer patients undergoing chemotherapy and radiotherapy may have failed, in part, because the provision of amino acids, particularly methionine and ornithine, may have facilitated tumor growth. Future studies might investigate support strategies which provide nutrients that the host can use for anabolism without enhancing tumor growth.

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ADDITIONAL INVESTIGATIONS

Dr. G.E. Catton, Director of the Ottawa Regional Cancer Centre, reports on the following clinical research investigations:

In 1986, 367 patients were entered on clinical trials at the Ottawa Regional Cancer Centre, and accrual in 1987 has remained active. Presently 81 active clinical protocols are accruing patients. The Centre is participating in NCIC, NSABP, pharmaceutical company, and local studies. These studies include adjuvant chemotherapy of breast cancer, osteogenic sarcoma, colorectal carcinoma, and non-small cell lung cancer. Studies combining chemotherapy with radiotherapy are underway in bladder carcinoma, glioblastomas, brain metastases, primary central nervous system lymphoma, advanced head and neck carcinoma, non-small and small cell lung cancer. Studies of chemotherapy in advanced or metastatic disease are underway in breast cancer, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, hairy cell leukemia, soft-tissue sarcoma, Kaposi's sarcoma, colon carcinoma, hepatocellular carcinoma, ovarian carcinoma, superficial bladder tumors, renal cell carcinoma, prostate carcinoma, testicular carcinoma, glioblastoma, brain metastases, head and neck carcinoma, non-small cell lung carcinoma, and small cell lung cancer. Also a number of Phase I studies, pharmacology studies, and a variety of tumor biology studies are underway. Radiotherapy studies are underway in breast cancer, non-small cell lung cancer, head and neck cancer, and carcinoma of the endometrium. Notable high points in the clinical research program have been the demonstration of a high complete remission rate when intra-arterial cisplatin is combined with radiotherapy for localized bladder cancer and the demonstration that weekly administration of the agent, menogaril, enables us to give the drug in a dose intensity more than twice as great as when the drug is given once every four weeks. On a once-weekly schedule, the results suggest that menogaril is effective in a number of different tumor types.

REPAIR AND INHIBITION OF REPAIR IN RADIATION-RESISTANT HUMAN CELL LINES BY HYPERTHERMIA

Investigators: G.P. Raaphorst, M. Feeley, V. Da Silva and J. Cygler

Human glioma cells are being evaluated for thermal and radiosensitivity. Three cell lines have been obtained and tested to date. It was found that these cell lines were highly radioresistant and demonstrated a large shoulder on the radiation survival curve. Further studies showed that the cells had a large capacity to repair radiation damage. The thermal senstitivity in these cell lines was not much different from that of normal human fibroblasts. However, hyperthermia was shown to enhance radiation sensitivity especially by reducing the shoulder of the radiation survival curve. This indicated potential for radiosensitization in the low-dose region, which is relevant to fractionated radiotherapy. Further study shows that hyperthermia could also inhibit the repair of potentially lethal damage

in these cells. This study is being extended to different time-temperature sequences of hyperthermia and radiation. In addition, we will examine other radiation-resistant and radiation-sensitive cell lines.

INTERACTION OF CHEMOTHERAPEUTIC AGENTS AND HYPERTHERMIA IN HUMAN GLIOMA CELL LINES

Investigators: V. Da Silva, G.P. Raaphorst and M. Feeley

We evaluated the sensitivity of three human glioma cell lines to three chemotherapeutic agents, namely, cis-platinum, BCNU, AZQ and SHM. All these agents had toxic effects in the human glioma cell lines. Two of the cell lines were BCNU-resistant and this resistance is being further evaluated. When hyperthermia was applied in combination with chemotherapeutic agents, hyperthermia caused sensitization to the toxic effects of the chemicals. Even in the BCNU-resistant cell line, thermo-chemosensitization was observed. These studies will continue in order to evaluate optimization of treatment temperatures and sequences and drug concentration. In addition, the role of GSH in chemo- and thermosensitization will be evaluated.

EFFECT OF LONIDAMINE COMBINED WITH RADIATION OR HYPERTHERMIA IN RODENT AND HUMAN CELLS

Investigators: M. Feeley, C.E. Danjoux, G.P. Raaphorst and B. Fisher

Lonidamine – a compound that inhibits energy metabolism in cells – was shown to cause radiosensitization and thermal sensitization of rodent cells. We are in the process of evaluating this agent in human cells. The effect of lonidamine was tested in glioma, melanoma and fibroblast human cells in culture and compared to the responses of Chinese hamster lung cells. The toxic effects of lonidamine were much less in human cells than in hamster cells. In addition, lonidamine inhibited repair of radiation damage and the fixation of radiation damage at high concentrations in rodent cells. So far we have not found that lonidamine inhibits repair of potentially lethal radiation damage in human glioma cells, melanoma cells and fibroblasts. In addition, lonidamine at various concentrations causes thermal sensitization indicating its possible use in clinical hyperthermia. Further studies with lonidamine will be done in other cell lines to determine if the radiosensitization it causes is specific to tumor type.

MEASUREMENTS OF RADIATION AND/OR HYPERTHERMIA EFFECTS IN RAT-BRAIN TUMORS USING H-1 AND P-31 NUCLEAR MAGNETIC RESONANCE (MR) SPECTROSCOPY

Investigators: G.P. Raaphorst, D. Wilkins, R. Kroeker and I. Smith

The response of mammalian tissue cells to cancer therapy can be reflected in changes in their metabolic status. Cellular metabolic state can be measured through P-31 spectroscopy by evaluating the levels of high-energy phosphate

metabolites in the cell. Presently we are building surface coils to perform P-31 and H-1 spectroscopy on the rat brain and on brain tumors. The tumor model is also being worked up in the laboratory. The equipment to apply hyperthermia is already available and a special small applicator has been designed to apply heating to volumes of approximately 1 cm^3. This project is being done in collaboration with the National Research Council of Canada and we will use the MR equipment in the laboratory of Dr. Ian Smith. The effect of radiation in combination with hyperthermia will be evaluated on tumor responses, and on responses in the normal brain. These data will provide guidance in similar experiments on the human nuclear MR imaging system when spectroscopy becomes available at the Ottawa General Hospital.

MEASUREMENT OF BREMSTRAHLUNG SPECTRA FROM IRRADIATORS FOR ELECTRON BEAMS 8-35 MeV

Investigators: D.O. Rogers, G.P. Raaphorst and B. Faddegon

This program is directed at defining Bremstrahlung data from high-energy accelerators. It will follow a systematic tabulation of relative and possibly absolute measurements in emitted photon energy and angle in the energy range of 8 to 35 MeV for different target-beam-flattener combinations of interest in medical physics and industry. In addition, the program will compare measured, thin-target spectra to current state-of-the-art theory and measured spectra from representative medical and industrial targets to Monte Carlo simulated spectra. The graduate student is working up detectors and familiarizing himself with the accelerator operation which are available at the National Research Council of Canada. In addition, the software for this program is available and the initial calculations are being made. This project, which is being done in collaboration with the National Research Council of Canada, will use equipment in the laboratory of D.O. Rogers.

COMPUTERIZED CLINICAL HYPERTHERMIA THERMOMETRY SYSTEM

Investigators: L.H. Gerig, G.P. Raaphorst, A. Ginsburg and C.E. Danjoux

A computerized data acquisition and control system has been designed to measure thermal distribution during clinical hyperthermia. The thermal transducers are type K or type T microthermocouple arrays, designed and produced inhouse. These thermocouple arrays provide up to 11 measurement points along a single track of outside diameter 0.8 mm. The automatic data acquisition system, which is capable of sampling up to 64 thermocouples, was designed to optimize the integrity and accuracy of temperature measurement, particularly in the presence of thermal gradients, and to minimize the problems associated with the use of thermocouples in an electromagnetic field.

BLOOD-FLOW STUDIES

Investigators: L.H. Gerig, G.P. Raaphorst, G. Forester, A. Ginsburg and C.E. Danjoux

A knowledge of blood flow and vascular response to thermal insult is central to the development of the bioheat equation and subsequently to thermal treatment planning. We are engaged in a series of experiments designed to look at thermally induced vascular compensation and damage in pigs. This work employs both radioactive microsphere and thermal washout techniques to measure blood flow. Early studies on pig muscle have shown that the blood flow increases as the temperature is increased. We are now extending this program to look at the visceral organs and the central nervous system.

CLINICAL APPLICATION OF HYPERTHERMIA TO SUPERFICIAL TUMORS

Investigators: C.E. Danjoux, L.H. Gerig, G.P. Raaphorst, S. Grimes and A. Ginsburg

Hyperthermia is being used in combination with radiotherapy in the treatment of superficial human cancer. It is applied using a 2450 MHz microwave generator and applicators customed designed at the National Research Council of Canada. The thermometry system used to record the treatment temperatures in the tumor area, which was designed at the Ottawa Regional Cancer Centre, consists of a series of interstitial microthermocouple probes connected to an IBM PC and Kiethly data acquisition system. To date 20 patients have been treated for superficial tumors at various sites. The clinical results show that the normal tissues tolerate combined hyperthermia and radiation very well. In addition, some tumors, which have not responded to full courses of radiotherapy, subsequently responded to a reduced course of radiotherapy combined with hyperthermia. Thermometry data has shown that tumors can be heated to therapeutic temperatures with our hyperthermia system and that both normal tissue and tumor respond to hyperthermia by increases in blood flow. These results are consistent with results being obtained in animals.

VERIFICATION OF THERAPLAN V 0.4 ELECTRON BEAM TREATMENT PLANNING ALGORITHM: COMPARISON OF CALCULATIONS WITH MEASUREMENTS IN AN ANTHROPOMORPHIC PHANTOM

Investigators: J. Cygler and J. Ross

Calculations done with Theraplan V 0.4 were compared with experimental data for simple geometry inhomogeneous phantoms and for anthropomorphic (Rando) phantoms. Semiconductor diodes were used to measure dose profiles in the former and TLD dosimeters were used to measure dose distribution in the latter. Studies of four different therapy set-ups were done at 6, 9, 13, 17 and 20 MeV electron energies. Doses in phantom sections containing regions of low-density inhomogeneities (lung tissues) were greatly overestimated (up to 40%). For sections containing regions of high density inhomogeneities, Theraplan was found to underestimate the dose by up to 10%.

AUTOMATED SELECTION OF MUTANT CELL LINES

Investigators: L.H. Gerig, D. Brown, G.P. Raaphorts and E. Petrio

Cell lines sensitive to therapeutic agents are valuable in the study of mechanisms of action. The development of such cell lines by mutagenesis and subsequent selection is a difficult process. We have completed a preliminary investigation of the feasibility of an optically based, mutant-cell-line selection system. The system employs a video camera and frame "grabber" interfaced to an IBM PC. We have demonstrated that it is able to measure colony size and growth and thus provide information on degree of cellular toxicity and division delay. As a result we are expanding the program in collaboration with the Department of Engineering at the University of Ottawa and hope to develop an automatic, robotized, mutant-cell-line selection system.

Northeastern Ontario Oncology Program

CLINICAL INVESTIGATIONS

Dr. R.E.T. Corringham, Director of the Program, reports on the following clinical research investigations:

At this time, the Northeastern Ontario Oncology Program (NEOOP) research program has two main aspects: A clinical trials group, which has an office in Sudbury; and an epidemiologist with the Division of Epidemiology and Statistics at Head Office in Toronto. The clinical trials group is participating in a number of trials and the program is involved in a number of epidemiological studies in Northeastern Ontario. NEOOP's own clinical trials are being entered and colated on MEDLOG, an electronic data-storage, retrieval and analysis system.

NEOOP, in collaboration with the Division of Epidemiology and Statistics, has completed a retrospective study of cancer mortality in Northeastern Ontario for 1974-1983. This study, which soon will be submitted for publication, shows a significantly higher mortality of cancer in Northeastern Ontario than in the rest of the province. Currently under consideration is a survey of cervical cancer screening in native Indian women on Manitoulin Island.

BREAST CANCER

We are entering patients into the NCIC MA.4 co-operative clinical trial of adjuvant postsurgical treatment of breast carcinoma in postmenopausal patients with histologically involved axillary nodes. Postmenopausal patients with advanced or recurrent breast carcinoma are being entered into a transCanada multicentre trial (Cyanamid), which is evaluating the use of Novantrone (mitoxantrone) as first-line therapy. This study is approaching completion.

HEMATOLOGICAL MALIGNANCIES

Patients with newly diagnosed multiple myeloma are being entered into the NCIC M4.6 trial. In this randomized control trial (RCT), patients are randomized between conventional therapy with or without the addition of alpha-interferon. NEOOP is conducting its own study of patients with refractory myeloma using a novel multidrug combination; early results look promising. Patients with Hodgkin's disease are being entered into the NCIC HD.4 trial -- an RCT, which will compare MOPP/ABV hybrid with alternating MOPP/ABVD for advanced or recurrent Hodgkin's disease.

LUNG CANCER

NEOOP has completed an inhouse pilot study of a new combination chemotherapy regimen in small cell lung cancer. Early results are sufficient to justify a larger trial which now is being organized. Also a pilot study is evaluating a novel multidrug chemotherapy protocol in non-small cell lung cancer.

GYNECOLOGICAL CANCER

NEOOP will enter patients with high risk endometrial cancer into a new OCOG study, which will randomize such patients between standard and wide-field radiation with or without medroxyprogesterone. This study will be conducted in collaboration with the Princess Margaret Hospital in Toronto where NEOOP patients will receive their radiation therapy. A pilot study is being developed to evaluate intraperitoneal chemotherapy in advanced ovarian cancer.

GASTROINTESTINAL MALIGNANCY

In patients with gastrointestinal malignancy NEOOP is conducting a pilot study of intrahepatic arterial chemotherapy given in an outpatient setting using computerized ambulatory drug delivery pumps. This form of therapy has proved to be feasible and safe but it is too early to comment upon its efficacy.

PORTACATH STUDY

NEOOP's nursing staff will evaluate the efficacy of normal saline versus heparinised saline in maintaining the patency of Portacath systems.

Toronto-Bayview Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. R.D.T. Jenkin, Director of the Toronto-Bayview Regional Cancer Centre, reports on the following clinical investigations:

DOSE MEASUREMENTS IN HIGH INTENSITY RADIATION FIELDS

Investigators: P.F. O'Brien, R.B. Barnett, H.B. Michaels and R.A. Siwek

Software faults on the Therac-25 linear accelerator have caused malfunction of this machine at several user sites. All of the failures were characterized by a mismatch of beam-control parameters and mode-dependent beam hardware, which resulted in the delivery of very large amounts of radiation in a very short time. All of the physicists at the Toronto-Bayview Centre participated in experimental investigations to determine the nature of the radiation field produced in this abnormal situation. Normally the dosimetry systems in radiotherapy centres are used over a very small range of doses and dose rates. In these circumstances, pulsed rates are in the range 0.1 to 0.01 cGy/pulse, and total dose rarely exceeds 8000 cGy. Before making measurements in radiation beams of unknown but high intensity, one must carefully consider the characteristics of the dosimeters employed. In these investigations, we have used chemical dosimeters, ionization chambers, thermoluminescent dosimeters and a water calorimeter and have measured total doses at isocentre of up to 20,000 cGy produced in about 0.5s.

SHIELDING EFFECTS OF SELECTRON APPLICATOR AND PELLETS ON ISODOSE DISTRIBUTIONS

Investigators: R.A. Siwek, P.F. O'Brien and P. Leung

The Selectron is a mobile, remote, afterloading device which was developed specifically to reduce the radiation exposure to hospital personnel during intracavitary brachytherapy. Our Selectrons each contain 18 cesium-137 sources -- each with an activity of approximately 0.74 GBq. Source trains of 48 spherical pellets per channel are composed of both active and inactive pellets, which have an external diameter of 2.5 mm. The configuration of pellets is in accordance with the required dose distribution and the patient's geometry.

Isodose distributions around a Selectron Fletcher-type applicator containing a typical patient loading of active pellets were measured and compared with those calculated by the AECL Theraplan Computer Planning System. The shielding effects of the stainless-steel applicator tubes, the ovoids, screws, inactive and active pellets were considered. The effects of scatter and attenuation by the pellets were illustrated by measured isodose distributions around a single applicator tube and by measurements of water-to-air ratios.

A calculational model has been proposed based on the separation of radiation into primary and secondary components. This model takes into account the absorption of the primary radiation by the pellets.

DOSIMETRY OF THE NEODYMIUM-YAG LASER IN THE PIG URETER

Investigators: R.A. Siwek, R. Kodama, J. Srigley and L. Klotz

The neodymium-yttrium-aluminum-garnet (Nd-YAG) laser has been successfully applied endoscopically to treat bladder neoplasms. In selected patients, well-differentiated tumors in the ureter would lend themselves to laser therapy. However, the wall of the ureter is thinner than that of the bladder and reduction of laser energy would be necessary. The ideal in laser irradiations is to optimize the distribution of delivered light to match the geometric and optical characteristics of the target tumor tissue, thus minimizing damage to surrounding normal tissue. No safe dosage guidelines have yet been established. It is our intention to determine suitable dosages.

To date we have reported our preliminary data of Nd-YAG therapy on the normal pig ureter. This was an acute study on laparotomized pig ureter. Various doses of laser radiation were delivered. Heat measurements at the peri-adventitial surface of the ureter were measured with thermocouples. Ureteral sections were examined histologically to determine the effect of the laser radiation.

Dosimetry data have been acquired in pig models over the last year. We have developed a formula by which tissue temperature may be calculated on the basis of irradiance and duration.

In the future we plan to establish the effect of healing after laser irradiation at various dosage levels. Using the data gained from the acute studies, radiologic and histologic data will be correlated with varying doses of laser energy administered under direct vision through the ureteroscope.

WATER CALORIMETRY

Investigator: R. Barnett

A water calorimeter (Domen, 1982) is being used to measure the absorbed dose from radiation beams of Co-60, high-energy x-rays, and electrons. The absorbed dose is determined from the product of the heat capacity of water and the temperature rise measured during irradiation. The water calorimeter has the potential to provide an absorbed-dose standard, which would be particularly useful for high-energy radiation dosimetry.

Measurements with a vented core (Barnett and Cormack, 1986) indicate that the measured temperature rise per monitor unit is variable for low accumulated dose but stabilizes for accumulated doses of typically 200 Gy. Using a sealed calorimeter, Ross et al (1984) reported that the temperature rise per monitor unit depends on various dissolved gases in water and on the accumulated dose. At the Toronto-Bayview Centre, calorimeter measurements are being taken to determine

the difference between a sealed and a vented core. Additional experiments will be done to determine the effect of deliberately adding contaminants, e.g. organic compounds, to the water. The purpose of this research is to determine the reliability of a water calorimeter as a field instrument.

PHYSICAL ASEPCTS OF HIGH-ENERGY PHOTON AND ELECTRON BEAMS IN LOW-DENSITY MATERIAL

Investigator: P.F. O'Brien

Measurements are being taken for both photon and electron beams to determine dose distributions in low-density material, and at the interface between low-density and unit-density material. Normally, electron transport effects for high-energy beams are not included in treatment planning algorithms and these effects may significantly alter the dose distribution from that obtained in a unit-density phantom. Initial measurements for electron beams are being compared with calculations done with a widely used electron pencil-beam model.

COLLECTION EFFICIENCY OF MONITOR ION CHAMBERS

Investigator: P.F. O'Brien

The aim of this project is to investigate the effects of incomplete ion collection in the monitor chamber on the dosimetry system of a linear accelerator. For many accelerators, the monitor chamber signal is used in a servo manner to control dose, dose rate and steering. Changes in pulse size or shape may produce changes in the chamber's collection efficiency and these changes may cause instability in the steering system and uncertainties in the machine's output. Initial measurements on a Therac-25 linear accelerator indicate that allowed changes in pulse size can produce sufficient change in the monitor's collection efficiency to alter the size of a monitor unit by 20%.

EFFFECT OF ELECTRON AFFINITY ON RADIOLYTIC OXYGEN DEPLETION IN SOLUTIONS OF NITROAROMATIC RADIATION SENSITIZERS

Dr. H.B. Michaels has continued his investigation of mechanisms of action on hypoxic cells of radiation-sensitizing drugs. Under certain conditions, these drugs interfere with the depletion of oxygen by radiation. These effects have been observed in irradiated aqueous solutions and in mammalian cells. Experiments have been extended to nitroimidazole and nitrofuran derivatives of widely varying electron affinity. The oxygen concentration in sealed solutions was monitored continuously with a sensitive oxygen electrode during irradiation. Significant protection of oxygen from radiolytic depletion was observed in concentrated solutions of nifurpipone – the most electron-affinic drug studied, while no such effect was observed for metronidazole – the least electron affinic-compound. The results are consitent with a model developed previously to explain the interaction of sensitizer and oxygen depletion on the millisecond time scale.

MEDICAL PHYSICS CONSIDERATIONS FOR TREATMENT OF MALIGNANCY WITH RADIOLABELLED MONOCLONAL ANTIBODIES

Dr. H.B. Michaels is responsible for the physical and radiobiological components of a collaborative study on the use of radiolabelled monoclonal antibodies in the treatment of patients with advanced ovarian carcinoma. These studies have been directed at practical and technological aspects of the treatment, including aspects of radiation protection. Patients receive a tracer dose, followed by a therapeutic dose, of antibody tagged with a radioactive isotope; the isotope being used is iodine-131. The radiation dosimetry for this type of treatment is very complex and is outside the realm of traditional dosimetric protocols. The dosimetry and radiobiology of this modality require intensive study and constitute a major research project.

University of Toronto

MEMBRANE ABNORMALITIES IN LEUKEMIA*

M.A. BAKER**, *Toronto, Ontario*

Structural and Functional Changes in Leukemia Secondary to Abnormal O-Linked Glycosylation

We have shown that aberrant sialylation of granulocyte membranes in chronic myelogenous leukemia (CML) may explain functional abnormalities of CML granulocytes. Lectin reactivity with normal and leukemic leukocytes suggested that sialylation was excessive on leukemic cells. This was confirmed by electrophoresis of membrane extracts following galactose oxidase or periodate oxidation and 3H-borohydride reduction. Abnormal sialylation was corrected by neuraminidase treatment, but sialylation patterns were quickly re-established in cultured cells. Incubation with retinoic acid inhibited regeneration suggesting that differentiation played a role in this phenomenon.

To examine the specificity of the glycosylation abnormalities, specific sialyltransferases were studied in CML and normal leukocytes. Of several sialyltransferases and galactosyltransferases measured, elevated activity was seen only with the enzyme that specifically sialylates GAlβ1-3GalNAc in the 2-3 position. Patients with CML receiving chemotherapy have a change in cell function that suggests reversion of the abnormal sialylation. Studies of the granulocyte membrane in treated and untreated patients suggest that both the structural and functional changes in CML are altered by chemotherapy. Most recently, studies of the enzyme-substrate product, using HPLC analysis, have confirmed the highly specific rise in enzyme activity in CML versus normal granulocytes.

Structural and Functional Features of a Cell-Surface Phosphoglycoprotein Associated with Tumorigenic Phenotype

Many attempts have been made to link malignant transformation to changes in the cell-surface phenotype. Phenotypic changes detected in malignancy have

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largely proven to be characteristic of a particular phase of normal differentiation and recently we have reviewed these changes in leukemia. Stanbridge and colleagues[1] have fused normal human fibroblasts to HeLa cells, obtaining hybrids that are non-tumorigenic in nude mice. Rare tumorigenic segregants arise, and Bicknell and co-workers[2] have raised monoclonal antibodies that recognize a structure on the tumorigenic segregants that is absent from the non-tumorigenic hybrid.

Recently, we characterized the structural and functional features of the compound associated with the tumorigenic phenotype. The molecule is a dimeric phosphoglycoprotein p75/150 which is glycosylated at both N-linked and O-linked sites. It was shown to be an integral membrane protein but without a large cytoplasmic domain. It appears to be covalently associated with fatty acid. Amino acid segments of tryptic peptides revealed no strong homology with known oncogene products or other proteins. The molecule was phosphorylated on serine and intrinsic phosphoserine kinase activity was demonstrated. Stanbridge et al are now attempting to clone the gene for this molecule.

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RECESSIVE CANCER MUTATIONS: THE RETINOBLASTOMA MODEL*

B.L. GALLIE**, *Toronto, Ontario*

Study of the rare tumor, retinoblastoma (RB), has revealed a basic mechanism by which tissue-specific genetic mutations lead to cancer[1]. In this unusual tumor, 40% of patients develop bilateral RB tumors because they have a heritable mutation that predisposes to RB in infancy. Most children with heritable RB are cured by surgery and radiation, but they are at risk to develop osteosarcoma as teenagers. The gene predisposing to RB has been mapped to chromosome 13q14, first by the observation of deletions of this region in patients with RB, and later by family studies linking RB and an enzyme marker on chromosome 13. Sixty per cent of RB patients develop only one tumor (unilateral) and do not transmit any hereditary tendency to the cancer.

Molecular analysis of RB tumors[2,3] has shown that cancer is initiated when both alleles at the chromosome 13q14 locus become mutant. In hereditary cases the first mutant allele is heritable, and the second arises in the retinal cells that become malignant; in non-heritable cases, both mutations arise in the same retinal cell. Thus, RB tumors will show a range in size of mutation, from large deletions involving adjacent genes in addition to the RB gene, to point mutations resulting in only a defective protein product.

Several other types of cancer have been shown to arise by mutation of both alleles of specific genes: on chromosome 13q for osteosarcoma[4] and some familial breast cancers; on chromosome 11p for Wilms' tumor and embryonal rhabdomyosarcoma; on chromosome 3p for small cell carcinoma of lung; and on chromosome 22 for bilateral acoustic neurofibromatosis.

A gene, "4.7R", recently cloned from chromosome 13q14[5] is completely deleted in some RB tumors, leading to the suggestion that this is the RB gene. We find that 12% of the 34 RB tumors show DNA deletion or rearrangement of 4.7R; 16% show abnormal size of messenger RNA; and by detailed study of RNA transcripts that should reveal even single-point mutations. Only the same 15% (5 out of 34) of tumors are abnormal.

Therefore, the range of size of mutations expected of the RB gene is not found for 4.7R. Rather, only a few (5) large rearrangements of 4.7R are observed, such as would occur if it were a close neighbour of the RB gene. However, this gene marker is the closest probe to RB yet identified and is a great advance in the effort to clone this human cancer gene. Once the true RB gene is identified,

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cloned and its protein product identified, analogous strategies can be applied to the other cancers that are initiated by similar mechanism.

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THE RELATIONSHIP OF PHEOMELANIN AND ULTRAVIOLET RADIATION IN CARCINOGENESIS*

H.F HABERMAN** and I.A. MENON†, *Toronto, Ontario*

Investigations continued into the assessment of factors involved in the etiology of skin cancer. Exposure to ultraviolet radiation, a major factor, was thought to reflect chiefly lesser amounts of melanin in the skin. Our studies have shown that the melanin from human red hair has properties different from the melanin from black hair. Ultraviolet irradiation of red hair melanin was found to produce reactive chemical species e.g. superoxide, hydrogen peroxide, free radicals, etc., which caused tissue damage. Controls using either the melanin from black hair or red hair melanin without ultraviolet radiation did not produce equivalent cell damage. We employed several biological parameters to assess the combined effects of ultraviolet radiation and melanin; among the effects observed were ultrastructural damage of cells, lesions in intracellular DNA, changes in cell membrane, decrease in cell viability and cell lysis. Our findings indicate that, in addition to the total amount of melanin, the type of melanin in the skin also is a factor in the etiology of ultraviolet radiation-induced skin cancer.

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EVALUATION OF A NUCLEAR ESTROGEN RECEPTOR ASSAY FOR HUMAN BREAST CARCINOMA*

G.E. MOBBS**, *Toronto, Ontario*

We have continued to collect data on the nuclear estrogen receptor (ER) content of breast cancer specimens from patients at Women's College Hospital in Toronto, using a monoclonal antibody for ER in an enzyme immunoassay (EIA), in addition to the assay of cytosolic ER and progesterone receptor (PgR) of the same specimens. Long-term follow-up of these patients should enable us to determine which of these assays (or combination of assays) gives the most accurate prediction of prognosis and/or hormonal sensitivity of the disease.

In addition, we are collecting similar data on experimental rat mammary carcinomas, induced with dimethylbenzanthracene. This tumor has been widely used as a model for the human disease, especially with regard to the hormonal control of growth. Because the response of these tumors to estrogen deprivation by ovariectomy is usually clear cut and occurs within a few weeks, it should be possible to determine relatively quickly whether assay of nuclear ER using the EIA technique adds to the predictive value of ER and PgR in predicting hormonal sensitivity in this model, thus supplementing the clinical data.

This project is supported by Women's College Hospital Research Fund.

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HORMONE RECEPTOR MECHANISMS IN THE DEVELOPMENT AND TREATMENT OF PROSTATIC NEOPLASIA*

G.E. MOBBS**, *Toronto, Ontario*

Four sublines (H, HI, G and AT) of the R3327 (Dunning) rat prostatic carcinoma have different androgen sensitivities and histopathological characteristics. To investigate whether these characteristics were associated with differences in the hormone receptor (HR) profile and its response to estrogen, we carried out Scatchard analysis on the cytosolic (C) and high-salt nuclear-associated (N) androgen, estrogen and progesterone receptor (AR, ER and PgR) in each line, carried in control and diethylstilbestrol (DES)-treated animals. In the H line (androgen-sensitive, well-differentiated), DES treatment resulted in significant increases in total cellular AR and ER, in redistribution of both receptors between the C and N fractions, and in a marked increase of PgR (>10 fold). The hormone receptor profile and its response to DES was similar in the HI line (androgen insensitive, well-differentiated), except that total cellular ER was not increased after treatment. The G line (androgen sensitive, poorly differentiated) contained higher basal concentrations of AR and PgR than the H line, but the concentrations were not increased by DES treatment, although treatment promoted association of ER with the nuclear fraction. The AT line (androgen insensitive, anaplastic) contained no ER and negligible PgR, but AR was present, although in lower concentrations than in the other lines. Diethylstilbestrol treatment had no effect on the concentration, although redistribution of AR between C and N fractions did occur. The AR in the AT line differed qualitatively from that in the H line in that dissociation from bound ligand was faster at 15°C, and progestins had a somewhat higher affinity for AR in the AT line than in the H line. However, injection of testosterone to castrated animals bearing the AT tumor promoted association of AR with the nuclear fraction, indicating normal activation, despite the lack of androgen sensitivity of this line.

The data suggest that the ability of DES treatment to increase AR and PgR concentrations is associated with differentiation and/or the presence of stroma, and is not associated with androgen sensitivity. Since high concentrations of PgR can be induced in the H and HI lines, and appear to be constitutive in the G line, development of a cytotoxic agent designed to bind to PgR may be a potentially valuable new approach to the therapy of prostatic carcinoma, irrespective of androgen sensitivity.

This project is supported by the National Institute of Canada.

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ROLE OF THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGF-R) AND ITS LIGANDS IN CANCER*

J.E. KUDLOW**, *Toronto, Ontario*

The EGF-R is a transmembrane protein which recognizes either EGF or transforming growth factor alpha (TGF-α) on the extracellular surface. The binding of either of these growth factors activates the internal domain of the receptor which is a protein kinase. Using monoclonal antibodies for the receptor protein and a cDNA probe for the receptor mRNA, we have shown in human breast cancer cells that receptor synthesis can be stimulated by phorbol ester tumor promoters, and by EGF or TGF-α. Similarly, using monoclonal antibodies for TGF-α and a cDNA probe, we have also shown that tumor promoter and EGF both stimulate TGF-α production in the same breast cancer cells. These results imply that once tumor promotErs have initiated the synthesis of the EGF-R and its activator – TGF-α – the cells continue to stimulate themselves to produce both receptor and growth factor.

We have also determined that TGF-α can be produced in normal tissues under hormonal control. Until we made these findings, it was believed that TGF-α was made exclusively by cancer cells. We have found TGF-α in the pituitary, ovary, and kidney. In the pituitary, TGF-α is in the same cells as prolactin and growth hormone, and its secretion can be stimulated by hypothalamic-releasing hormones. In the ovary, TGF-α is found in the interstitial cells and its secretion can be increased by pituitary hormones. These studies on cancer and normal cells are giving insight into the role of growth factor in hormonal control of cellular growth.

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RESEARCH UNIT OF THE DIVISION OF EPIDEMIOLOGY AND STATISTICS OF THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION*

E.A. CLARKE**, N. KREIGER† and L.D. MARRETT‡
Toronto, Ontario

The Epidemiology Unit of the Division of Epidemiology and Statistics has been affiliated with the Department of Preventive Medicine and Biostatistics at the University of Toronto since 1978. The Unit was established to conduct analyses using the cancer data bases of the OCTRF, to assess the quality of these data, to provide cancer researchers with epidemiological and biostatistical assistance, to conduct or support cancer research projects, and to provide information to the general public and the scientific community to increase their understanding of cancer.

Members of the Unit, holding academic appointments at the University, are Drs. E.A. Clarke, N. Kreiger, and L.D. Marrett. Other staff members are G. Cameron, P. Disenhouse, I. Fan, S. Guidici, S. Hilditch, N. Platt, N. Ryan, Y. Sullivan and M. Swift.

Externally-funded etiologic case-control studies of malignant melanoma, breast cancer, renal cell carcinoma, thyroid cancer, and fracture in postmenopausal women are in progress or recently have been completed. For some of these, the Ontario Cancer Registry is being used to ascertain appropriate cancer cases. The study of thyroid cancer is the first to be conducted by the newly-formed Canadian Cancer Registries Epidemiological Research Group, which includes cancer registries in all provinces.

Studies of second primary cancers continue in collaboration with the International Agency for Research in Cancer, most recently to assess the association between chemotherapeutic agents used to treat Hodgkin's disease, ovarian cancer, or testicular cancer, and the development of a second primary cancer.

A cohort of patients with Hodgkin's disease is being followed so that survival over a 15-year period can be assessed.

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*Project 381

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In collaboration with the City of Toronto Department of Public Health, a comparative, neighbourhood, historical cohort study has been conducted to estimate the effect of industrial pollution on the cancer rate of residents. The Ontario Cancer Registry was used to determine the cancer experiences of the neighbourhoods being compared.

Analyses are being carried out using data collected during case-control studies conducted by Epidemiology Research Unit staff in past years. These include examination of the association between cigarette smoking and endometrial cancer; the relationship between cervical neoplasia and oral contraceptive use, with particular emphasis on issues of bias and confounding; the association of cervical cancer with herpes simplex virus type II infection and cigarette smoking, in collaboration with researchers at McMaster University. Also, an evaluation of cervical cancer and dysplasia screening programs is being conducted collaboratively with researchers at McMaster University.

Finally, microcomputer software has been developed to display the data being generated by the Ontario Cancer Registry. These include graphs of time trends in the incidence or mortality of various types of cancer; maps of cancer mortality by county; and calculation of rates for specific subgroups. These have been useful in investigating the patterns of cancer in Ontario.

This project is supported by the OCTRF; and by grants, contracts, and career awards from the Ontario Ministry of Health; Health and Welfare Canada; National Cancer Institute of Canada; International Agency for Research on Cancer; and the Boston Drug Epidemiology Unit.

OCF

Windsor Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. G.K. Mok, Director of the Windsor Regional Cancer Centre, reports on the following clinical research investigations:

BREAST CANCER

We are active participants in the OCOG Stage I breast cancer clinical trial to evaluate the value of breast irradiation in patients who have had lumpectomies with negative axillary dissections.

We participated in the recently closed OCOG Stage II adjuvant chemotherapy study – 12 weeks versus 36 weeks of chemotherapy. Data is being compiled.

Patients also are being entered into the NCIC MA-4 trial. This is a Stage II adjuvant breast study comparing tamoxifen versus tamoxifen with CMF every three weeks for a total of eight treatments.

Our medical oncology group is conducting a study on DHAD (Novantrone) for advanced breast cancer. On the completion of this study, we intend to enter the new patients with advanced breast cancer to the NCIC IND-35 – CMF/Ionidamine.

CARCINOMA OF THE OVARY

We entered patients to the NCIC OV-8 ovarian cancer study to compare cis-platinum and cyclophosphamide versus carboplatinum and cyclophosphamide in Stage IV carcinoma of the ovary.

ENDOMETRIAL CARCINOMA

We also participate in the OCOG clinical trial to evaluate medroxyprogesterone and extended field irradiatin in high risk Stage I, II and III cases. We expect to enter our patients into this study in the near future.

MYELOMA

We have ethics approval for the NCIC MY-5 and MY-6 clinical trials in myeloma. However, we do not have qualified patients to enter into this study to date.

BROCHOGENIC CARCINOMA

We are active participants in the NCIC IND-33 protocol for advanced oat cell bronchogenic carcinoma using epirubicin intravenously every three weeks.

HODGKIN'S DISEASE

Our Hodgkin's disease program incorporates the NCIC HD-4 trial for advanced or recurrent disease.

SARCOMA

We are also participating in the NCIC IND-29 clinical trial on advanced soft tissue sarcoma using Adriamycin, DTIC and ifosphamide.

We are still affiliated with the SWOG in clinical trials. However, we have concentrated our main efforts to the NCIC trials during the past year.

EPIDEMIOLOGY AND STATISTICS

CANCER INCIDENCE, MORTALITY AND TREATMENT IN ONTARIO

E.A. CLARKE, M.B. B.S., M.Sc.*
N. KREIGER, M.P.H., Ph.D.** and
L.D. MARRETT, Ph.D.**
Toronto, Ontario

The Division of Epidemiology and Statistics is responsible for the adequate reporting of cases and the recording and compilation of data: One of the mandates of the Foundation under the Cancer Act. In pursuit of these objectives, the Foundation has maintained and improved a uniform case-recording system which was adopted by the regional cancer centres in 1947 and by the Ontario Cancer Institute incorporating the Princess Margaret Hospital (OCI/PMH) in 1957. The data from the regional cancer centres and the OCI/PMH are in machine-readable form from 1960 onwards. In addition to these records, the Foundation's computerized cancer-data base contains individual records on residents of Ontario who died from cancer since 1950; tabulations of deaths by sex, five-year age groups, and type of cancer from 1931 to 1986; individual records of patients diagnosed as having cancer in the Province between 1964 and 1985; individual records of hospital discharges on patients with cancer from 1964 to 1986; and pathology reports on specimens with cancer from 1972 to 1986. The total volume of records, in excess of three million, provides the Division with a unique opportunity for descriptive cancer epidemiology and allows the Division to assist other cancer researchers in the investigation of possible carcinogenic effects of exposure to occupational and environmental agents.

Most of the staff of the Division are located in the Head Office at 7 Overlea Blvd., but the Epidemiology Research Unit of the Division is located in the Department of Preventive Medicine and Biostatistics at the University of Toronto. Drs. Clarke, Kreiger and Marrett have cross-appointments in that department. This arrangement allows the staff of the Division to interact with other members of the epidemiological community and with medical and oncological colleagues.

In addition to the analyses of cancer incidence and mortality in the Province, the staff of the Division are involved in a number of other projects. Some are collaborative, using Ontario Cancer Registry data, with such agencies as the International Agency for Research in Cancer. Other studies are field studies conducted principally out of the Epidemiology Research Unit. Most of the case-control studies are supported by peer-reviewed grants.

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CANCER INCIDENCE AND MORTALITY

The Ontario Cancer Registry

The Ontario Cancer Registry now has 22 years of incidence data for the Province. The Registry now comprises information on more than 500,000 cases of cancer diagnosed in residents of Ontario between 1964 and 1985.

The Ontario Cancer Registry employs a unique system of registration, based on computerized record linkage on cancer cases collected routinely for other purposes and provided to the Foundation. The Registry receives more than 200,000 such records annually. The following province-wide data are routinely forwarded to the Registry:

1. Hospital discharges with a mention of cancer collected by the Hospital Medical Records Institute (HMRI) and supplied by the Ontario Ministry of Health: 100,000 computerized records per year.
2. Pathology reports with a mention of cancer submitted voluntarily by hospital pathology laboratories: about 35,000 paper records per year.
3. Reports on patients referred to the regional cancer centres and the OCI/PMH: 20,000 computerized records per year.
4. Deaths from all causes supplied by the Registrar General of Ontario: 65,000 computerized records per year.

Once source files are preprocessed, cancer incidence data are created in two major phases. First, sequential computer linkage of the source files is carried out to bring all records pertaining to an individual together. Then, a set of computerized rules called "case resolution" is applied to the linked records, to determine site of disease, histology, and date and method of diagnosis. Manual resolution is carried out routinely to deal with problems arising as a result of either linkage or case resolution.

To link together the large volume of data, the Foundation staff have developed a sophisticated computer record linkage system based on the Generalized Iterative Record Linkage System (GIRLS), designed by Statistics Canada in conjunction with the Epidemiology Unit of the National Cancer Institute of Canada.

"Case resolution" consists of a set of computer programs, developed by Foundation staff, which apply medical logic to determine the appropriate site of disease, histology, and date of diagnosis. Cases may be supported by one or many source records; some cases may have only a pathology report or a death certificate; some may have several hospital discharges, several pathology reports, and several treatment centre reports. Obviously, the number of sources of records contributing to a case will determine the quantity and quality of data available on that cancer diagnosis.

The generation by the Foundation of cancer incidence data for Ontario is a joint effort between the staffs of the Division of Epidemiology and Statistics and Information Systems who, together, have developed these systems of record linkage and case resolution.

All incidence data presented are given according to the International Classification of Diseases, Ninth Revision (ICD9). While originally the Registry had coded the cancer sites according to the Eighth Revision of the ICD between 1964 and 1978, all records now have been converted to ICD9.

Cancer Incidence and Mortality, 1985

Incidence data are described as provisional because they are based only on pathology reports and hospital records. In 1988, these data will be linked with death records and data from the regional cancer centres. As a result, frequencies and rates may not exactly reflect cancer occurrence in Ontario by a few percentage points.

Currently the time lag between cancer diagnosis and publication of incidence data by the Ontario Cancer Registry is about two years. There is a delay until the essential data have been provided by the sources, then it is necessary to code pathology reports, edit and process the files as described. Thus, the most current cancer incidence data available are for 1985; these are presented in Tables I through IV and Fig. 1. Although last year's report gave cancer mortality data for 1985, we show them again in Tables III and IV, and Fig. 1, to facilitate comparisons between incidence and mortality for the same year.

Tables I and II give the frequencies by 5-year age group for each cancer site or group of sites, for males and females respectively, for 1985. Rank order is given in the far right-hand column to aid in quick identification of sites of most frequent occurrence. Cancer of the cervix was overreported in 1985 by about 10% because some cases of non-invasive disease were reported; this problem will be corrected later in 1988. Fig. 1 indicates the frequencies of cancer for selected sites and causes of death for both sexes in 1985. We have included the 10 most common sites, in terms of their sex-specific incidence frequencies; they are ordered according to their sex-specific incidence frequencies.

Tables III and IV present incidence and mortality rates by age group and site, for males and females respectively, for 1985. The rates for 15-year age groups and for all ages are age-adjusted, using the World Standard Population shown in Table VII. Description of the method of direct age-adjustment used here can be found in *Cancer Incidence in Five Continents*, vol. 4, by Waterhouse et al. Rates in the table have been "age-adjusted" to assist comparisons between the different areas. Adjustment for age is used to account for differences caused solely by differences in the age distribution in these areas. The rates shown in Tables III and IV can be compared with any other rates covering the same age span and

using the same standard population for adjustment.

The "cumulative risk" (0-74), shown in the final column of Tables III and IV, is described in detail in *Cancer Incidence in Five Continents*. It is expressed per 100 and is a reasonable approximation to the risk to age 74 of being diagnosed with or dying of the given cancer. Thus, if the current age-specific rates for female lung cancer were to remain unchanged throughout her life, a girl born in 1985 would have about a 3% chance of receiving the diagnosis of lung cancer by age 74. Of course, if age-specific rates continue to rise, the cumulative risk will increase also.

Cancer Mortality, 1986

The most current cancer mortality data available are for 1986; these were provided by the Office of the Registrar-General of Ontario. Figs. 2 and 3 show the frequencies of death due to malignant neoplasms of all types relative to other major groups of causes of death. Tables V and VI give the numbers of cancer deaths by age group at death and site; the same format and groupings are used in Tables I and II for cancer incidence.

Populations

Table VII shows sex- and age-specific population data for Ontario for the years 1985 and 1986, and for the "world standard". The 1985 Ontario population (post-censal estimate) and the 1986 Ontario population (censal) are provided for those who would like to calculate age-specific cancer incidence and mortality rates from data tabulated in the previous sections. The world population is an artificial standard, frequently used in the calculation of age-adjusted rates. The Ontario population data are provided by Statistics Canada, and the world population is taken from *Cancer Incidence in Five Continents*.

CANCER TREATMENT

Hospital Caseload

During the Ontario Ministry of Health's fiscal year 1985-86, there were 72,178 separations (discharges and deaths) from active and rehabilitation hospitals in Ontario in which the primary diagnosis was cancer. These accounted for 5.4% of all hospital separations and 1,089,342 days of hospital care. The average length of stay for cancer patients declined from 16.9 days in 1972 to 15.4 days in 1985-86*.

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*Hospital statistics 1985-1986 published by the Ontario Ministry of Health

TABLE I

Annual Number of New Cases of Malignant Neoplasms in Males by Site of Disease and Age at Diagnosis, Ontario 1985 (Provisional Data*)

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	1	0	0	1	2	3	5	7	10	15	34	55	49	36	35	69	0	322	
Pharynx	146-148	0	0	0	2	1	1	2	7	10	10	12	19	26	18	15	14	0	137	
Esophagus	150	0	0	0	0	0	0	0	0	4	9	12	34	45	29	28	50	0	211	
Stomach	151	0	0	0	0	0	0	2	6	9	20	34	55	56	72	85	156	0	495	7
Intestine, except rectum	152,153	0	0	1	0	1	4	10	18	23	54	103	181	253	292	300	499	0	1,739	3
Rectum and anus	154	0	0	0	0	1	2	5	4	19	23	46	69	98	118	86	165	0	636	5
Pancreas	157	0	0	0	0	0	1	2	1	7	13	23	45	64	58	71	127	0	412	9
Nasal cavities, middle ear and accessory sinuses	160	0	1	0	1	0	0	1	2	1	1	1	3	5	3	1	7	0	27	
Larynx	161	0	0	0	0	0	1	0	0	4	9	30	51	48	45	36	34	0	258	
Trachea, bronchus and lung	162	0	0	0	0	2	3	5	18	46	83	235	396	558	591	500	646	0	3,083	1
Bone	170	0	1	9	7	5	2	2	5	3	1	2	1	8	5	3	12	0	66	
Connective tissue	171	0	1	4	2	4	6	6	3	6	8	8	15	15	11	5	18	0	112	
Malignant melanoma of skin	172	0	0	1	0	2	3	10	21	15	18	27	26	30	29	12	29	0	223	
Prostate	185	1	0	0	0	0	0	0	1	2	10	41	108	276	433	523	1,079	1	2,475	2
Testis	186	0	1	1	12	40	30	46	32	13	12	10	7	2	1	1	4	0	212	
Bladder	188	0	1	0	2	3	4	5	9	14	29	81	109	167	171	199	344	0	1,138	4
Kidney and other urinary	189	11	0	0	0	1	2	2	6	18	29	46	51	81	58	63	86	0	454	8
Brain and other nervous system	191,192	14	9	7	8	13	12	20	16	29	21	22	48	57	36	23	39	0	374	10
Thyroid gland	193	0	1	1	1	4	10	8	11	4	2	8	9	6	6	3	5	0	79	
Lymphosarcoma and reticulosarcoma	200	0	1	3	4	8	4	5	10	14	14	15	36	35	46	36	48	0	279	
Hodgkin's disease	201	0	3	2	21	18	17	14	9	5	6	5	11	5	6	9	6	0	137	
Other lymphomas	202	3	1	2	2	4	2	8	13	18	20	23	21	25	34	32	48	0	256	
Multiple myeloma	203	0	0	0	0	0	0	0	2	4	5	10	27	28	42	35	61	0	214	
Leukemia	204-208	28	14	7	16	10	7	6	13	10	11	28	38	42	61	78	148	0	517	6
Other and non-specific	Residual	15	4	4	6	13	8	13	25	32	68	85	132	220	194	175	380	0	1,374	
TOTAL	140-208[3]	73	38	42	85	132	122	177	239	320	491	941	1,547	2,199	2,395	2,354	4,074	1	15,230	

*See Text.
[1]ICD9 International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2]Rank order for 10 most common sites (or site groups).
[3]Excluding non-melanotic skin cancers (ICD9 number 173).

TABLE II

Annual Number of New Cases of Malignant Neoplasms in Females by Site of Disease and Age at Diagnosis, Ontario 1985 (Provisional Data*)

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	0	0	1	0	0	3	1	6	10	9	14	21	18	25	21	55	0	184	
Pharynx	146-148	0	0	0	0	0	0	0	2	3	1	6	8	3	9	6	12	0	50	
Esophagus	150	0	0	0	0	0	0	0	0	1	5	1	12	17	8	17	48	0	109	
Stomach	151	0	0	0	0	0	3	4	10	3	9	20	21	33	38	43	134	0	318	
Intestine, excepi rectum	152,153	0	0	2	2	2	5	5	20	53	51	90	160	228	265	259	637	0	1,779	2
Rectum and anus	154	0	0	0	0	0	1	5	6	12	13	31	36	60	83	64	195	0	506	6
Pancreas	157	0	0	0	0	0	0	1	4	4	9	13	33	36	63	48	157	0	368	10
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	1	0	1	1	0	3	0	4	0	5	3	7	0	25	
Larynx	161	0	0	0	0	0	0	0	0	1	5	4	6	7	6	8	7	0	44	
Trachea, bronchus and lung	162	0	0	0	0	0	2	4	16	38	73	111	188	221	259	191	281	0	1,384	3
Bone	170	0	2	6	6	1	4	1	2	1	1	0	2	1	4	2	12	0	45	
Connective tissue	171	0	1	2	5	2	4	5	3	5	11	4	8	8	6	6	26	0	96	
Malignant melanoma of skin	172	0	0	1	4	6	4	17	24	23	20	21	21	18	20	21	42	0	242	
Breast	174	1	0	1	1	2	24	90	188	298	326	441	483	508	446	416	773	0	3,998	1
Cervix uteri	180	0	0	0	1	6	34	56	68	54	33	37	41	48	34	21	44	0	477[4]	7
Body of uterus	182	0	0	0	0	0	1	3	15	20	39	91	142	190	153	133	141	0	928	4
Other and unspecified uterus	179,181	0	0	0	1	1	1	1	0	3	7	4	5	8	2	4	13	0	50	
Ovary and fallopian tube	183	1	1	1	4	6	13	13	26	24	51	54	81	107	87	74	114	0	657	5
Bladder	188	1	0	0	1	0	3	1	5	6	10	19	35	43	45	58	165	0	392	9
Kidney and other urinary	189	7	1	1	0	0	0	1	6	12	17	19	36	45	44	34	69	0	292	
Brain and other nervous system	191,192	11	4	9	9	11	8	4	13	14	11	32	29	38	33	35	47	0	308	
Thyroid gland	193	0	0	2	7	15	30	32	22	24	16	20	26	22	16	10	20	0	262	
Lymphosarcoma and reticulosarcoma	200	0	0	1	1	1	2	4	4	7	11	13	23	21	32	26	68	0	214	
Hodgkin's disease	201	0	1	5	16	15	14	9	9	3	1	4	4	6	5	4	7	0	103	
Other lymphomas	202	1	0	1	3	4	2	6	8	12	14	10	22	32	39	29	61	0	244	
Multiple myeloma	203	0	0	0	0	0	0	0	1	0	4	11	17	24	28	42	78	0	205	
Leukemia	204-208	21	12	16	4	4	7	7	11	13	9	12	23	35	34	47	143	0	398	8
Other and non-specific	Residual	11	2	1	2	7	15	20	16	30	37	61	100	144	125	177	471	0	1,219	
TOTAL	140-208[3]	54	24	50	67	84	180	291	486	674	796	1,143	1,587	1,921	1,914	1,799	3,827	0	14,897	

*See Text.
[1]ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2]Rank order for 10 most common sites (or site groups).
[3]Excluding non-melanotic skin cancers (ICD9 number 173).
[4]Approximately 10% non-invasive cancer of the cervix.

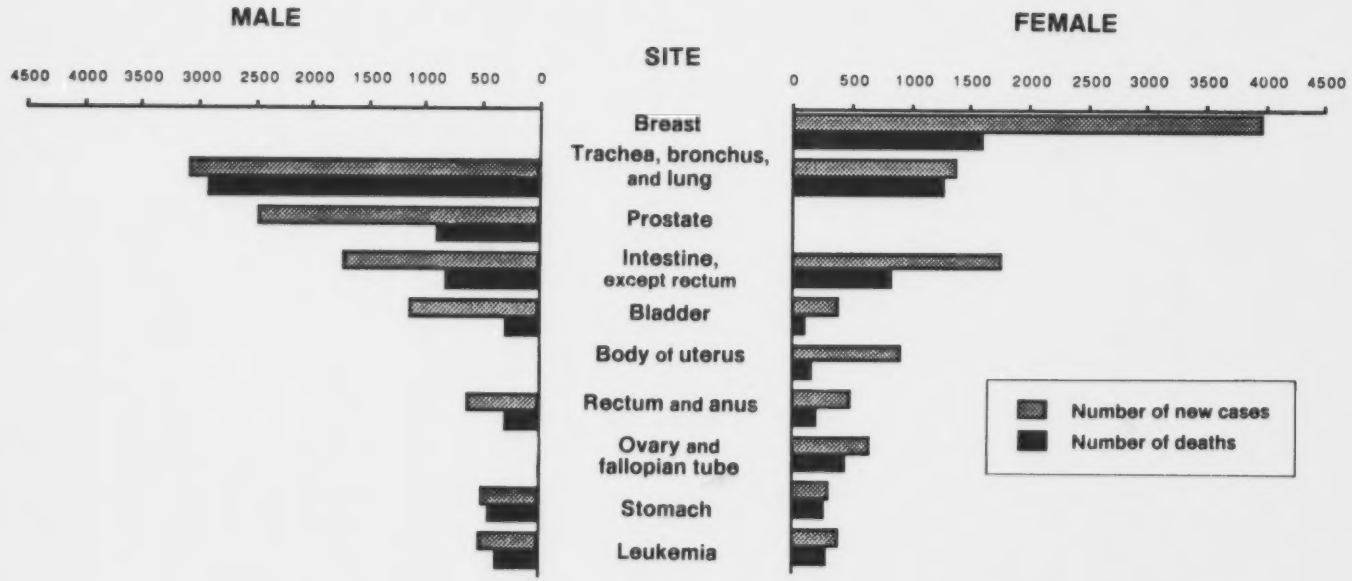

Fig. 1 New cases of, and deaths due to, malignant neoplasms, by sex and site of disease, for common cancers, Ontario 1985.

TABLE III

Age-adjusted Rates[1] and Cumulative Risks (age 0-74)[2] Incidence (I) and Mortality (M) from Malignant Neoplasms in Males, by Site and Age, Ontario 1985

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral cavity	140-145	I	0.1	0.5	2.3	13.8	25.7	50.2	6.0	0.66
		M	0.0	0.1	0.3	5.6	12.2	28.9	2.6	0.29
Pharynx	146-148	I	0.0	0.4	2.0	5.6	12.7	10.3	2.6	0.31
		M	0.0	0.1	0.8	3.0	7.8	7.3	1.5	0.18
Esophagus	150	I	0.0	0.0	0.5	7.2	21.9	35.5	3.8	0.46
		M	0.0	0.0	0.9	9.1	27.3	43.9	4.9	0.60
Stomach	151	I	0.0	0.0	1.8	14.6	44.9	111.6	8.8	1.00
		M	0.0	0.2	1.2	9.5	41.2	126.4	7.9	0.84
Intestine, except rectum	152,153	I	0.1	0.4	5.3	45.0	179.2	355.6	31.1	3.65
		M	0.0	0.1	2.5	18.5	75.5	229.1	14.6	1.60
Rectum and anus	154	I	0.0	0.2	3.1	18.5	64.8	116.1	11.5	1.35
		M	0.0	0.0	0.9	5.7	25.0	85.8	5.0	0.52
Pancreas	157	I	0.0	0.1	1.1	10.7	40.8	93.2	7.4	0.85
		M	0.0	0.1	1.7	10.0	45.7	113.1	8.2	0.94
Larynx	161	I	0.0	0.1	0.5	11.8	27.7	24.3	4.9	0.63
		M	0.0	0.0	0.2	3.7	12.5	16.9	2.1	0.27
Trachea, bronchus and lung	162	I	0.0	0.4	7.6	94.0	352.6	457.8	56.5	6.98
		M	0.0	0.2	5.1	76.6	321.3	558.2	52.5	6.29
Bone	170	I	0.9	1.2	1.0	0.6	3.5	8.6	1.3	0.11
		M	0.1	0.8	0.2	0.1	1.1	2.6	0.4	0.03
Malignant melanoma of skin	172	I	0.1	0.4	4.7	9.9	15.5	21.4	4.3	0.48
		M	0.0	0.2	2.3	4.0	10.3	18.2	2.4	0.25
Prostate	185	I	0.1	0.0	0.3	20.3	258.6	798.1	42.4	4.63
		M	0.0	0.0	0.0	4.0	72.3	402.0	15.2	1.34
Testis	186	I	0.2	6.6	8.7	4.2	0.9	3.4	4.1	0.31
		M	0.0	0.3	0.8	0.3	1.1	1.3	0.4	0.04
Bladder	188	I	0.1	0.8	3.0	29.2	113.5	252.7	20.4	2.35
		M	0.0	0.0	0.2	4.0	26.5	113.6	5.3	0.53
Kidney and other urinary	189	I	1.3	0.2	2.9	17.4	43.0	61.4	8.7	1.00
		M	0.1	0.1	1.2	7.1	17.4	38.2	3.7	0.43
Brain and other nervous system	191,192	I	3.2	2.7	6.7	12.3	25.2	27.0	7.5	0.75
		M	0.7	1.5	2.8	8.0	21.8	17.0	4.6	0.54
Thyroid gland	193	I	0.2	1.2	2.2	2.5	3.3	3.7	1.5	0.14
		M	0.0	0.0	0.0	0.4	0.8	4.2	0.2	0.02
Lymphosarcoma and reticulosarcoma	200	I	0.4	1.3	3.0	8.7	25.0	32.4	5.2	0.61
		M	0.1	0.3	0.5	1.2	5.6	14.7	1.2	0.12
Hodgkin's disease	201	I	0.5	4.8	2.7	3.0	4.2	3.9	2.8	0.24
		M	0.0	0.9	0.7	0.8	3.4	2.3	0.8	0.09
Other lymphomas	202	I	0.6	0.7	4.1	9.1	19.3	34.2	4.9	0.53
		M	0.2	0.7	1.4	6.9	17.7	33.5	3.8	0.44
Multiple myeloma	203	I	0.0	0.0	0.7	5.4	22.4	45.5	3.9	0.46
		M	0.0	0.0	0.5	2.4	13.9	31.2	2.3	0.28
Leukemia	204-208	I	5.4	2.9	3.0	10.3	37.9	106.9	10.0	0.97
		M	1.0	1.6	2.6	6.7	28.1	93.5	6.6	0.67
TOTAL	140-208[4]	I	16.4	28.2	76.2	397.9	1,477.0	2,953.0	277.5	27.33
		M	2.6	8.0	29.8	211.7	875.5	2,227.4	163.3	16.81

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.
[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research of Cancer (IARC) Scientific Publication No. 15, pp. 443-52, 1976).
[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

TABLE IV

Age-adjusted Rates[1] and Cumulative Risks (age 0-74)[2] Incidence (I) and Mortality (M) from Malignant Neoplasms in Females, by Site and Age, Ontario 1985

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral cavity	140-145	I	0.1	0.2	1.8	5.9	11.5	22.4	2.8	0.31
		M	0.0	0.0	0.3	2.7	4.2	13.6	1.1	0.11
Pharynx	146-148	I	0.0	0.0	0.5	1.9	3.2	5.0	0.8	0.09
		M	0.1	0.0	0.0	1.6	1.8	2.7	0.5	0.05
Esophagus	150	I	0.0	0.0	0.1	2.3	7.4	18.8	1.4	0.16
		M	0.0	0.0	0.0	0.9	6.4	23.3	1.2	0.12
Stomach	151	I	0.0	0.2	1.6	6.8	20.2	53.4	4.3	0.46
		M	0.0	0.0	0.6	4.2	15.9	55.0	3.3	0.35
Intestine, except rectum	152,153	I	0.2	0.8	8.6	39.7	134.3	256.2	24.9	2.88
		M	0.0	0.1	2.2	14.4	51.5	165.0	10.5	1.11
Rectum and anus	154	I	0.0	0.1	2.4	10.7	37.3	78.1	7.0	0.79
		M	0.0	0.0	0.5	3.8	13.4	44.2	2.8	0.29
Pancreas	157	I	0.0	0.0	0.9	7.1	26.3	63.3	4.9	0.55
		M	0.0	0.0	0.9	8.0	31.8	72.8	5.7	0.67
Larynx	161	I	0.0	0.0	0.1	2.1	3.7	2.8	0.7	0.09
		M	0.0	0.0	0.1	0.3	2.2	2.3	0.3	0.04
Trachea, bronchus and lung	162	I	0.0	0.2	6.3	49.5	121.6	115.3	21.9	2.73
		M	0.0	0.1	5.8	37.4	116.0	122.9	19.6	2.48
Bone	170	I	0.8	1.0	0.4	0.4	1.3	4.5	0.8	0.06
		M	0.3	0.1	0.0	0.1	0.5	1.5	0.2	0.02
Malignant melanoma of skin	172	I	0.1	1.2	6.4	8.7	10.5	17.3	4.1	0.41
		M	0.0	0.2	2.0	3.2	3.8	9.3	1.4	0.14
Breast	174	I	0.2	2.2	60.5	172.5	247.3	313.8	65.9	7.14
		M	0.0	0.4	12.9	55.3	112.9	184.1	24.6	2.79
Cervix uteri	180	I	0.0	3.3	17.6	15.5	19.1	18.2	8.4	0.82
		M	0.0	0.6	3.3	6.1	11.0	13.9	2.9	0.32
Other uterus	179,181,182	I	0.0	0.3	4.5	38.1	89.0	61.9	15.9	2.01
		M	0.0	0.0	0.3	3.1	13.6	34.7	2.4	0.27
Ovary & other uterine adnexa	183	I	0.3	1.9	6.4	25.5	48.7	46.1	10.9	1.25
		M	0.1	0.4	2.9	13.3	36.3	51.2	6.9	0.84
Bladder	188	I	0.1	0.3	1.3	8.4	25.7	66.0	5.2	0.58
		M	0.0	0.0	0.0	1.5	5.2	31.7	1.3	0.11
Kidney and other urinary	189	I	1.1	0.0	2.1	9.7	22.4	28.3	4.7	0.54
		M	0.3	0.3	0.2	2.2	10.0	22.6	1.9	0.21
Brain and other nervous system	191,192	I	2.7	2.4	3.2	9.7	19.0	18.9	5.6	0.57
		M	0.4	0.9	1.9	6.9	15.6	15.3	3.5	0.40
Thyroid gland	193	I	0.2	4.3	7.7	8.5	8.9	7.9	4.7	0.44
		M	0.0	0.0	0.0	0.6	1.7	5.7	0.4	0.04
Lymphosarcoma and reticulosarcoma	200	I	0.1	0.3	1.6	6.3	14.2	27.9	3.2	0.36
		M	0.2	0.0	0.0	1.2	3.3	12.1	0.8	0.08
Hodgkin's disease	201	I	0.6	3.9	2.0	1.2	2.7	2.8	2.0	0.16
		M	0.0	0.2	0.2	0.7	1.8	1.7	0.4	0.05
Other lymphomas	202	I	0.2	0.8	2.7	6.3	18.1	24.7	3.8	0.43
		M	0.2	0.1	0.8	3.5	13.3	30.3	2.6	0.29
Multiple myeloma	203	I	0.0	0.0	0.1	4.2	16.3	31.3	2.7	0.34
		M	0.0	0.0	0.2	2.8	10.9	28.3	2.0	0.24
Leukemia	204-208	I	5.4	1.3	3.2	5.8	20.4	57.5	6.4	0.57
		M	1.2	1.4	2.6	4.6	15.6	49.7	4.3	0.40
ALL SITES[4]	140-208[4]	I	14.0	27.7	150.2	477.3	1012.7	1544.2	231.9	23.03
		M	3.3	5.3	41.2	198.6	559.6	1170.4	113.3	12.10

[1]Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.
[2]Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research of Cancer (IARC) Scientific Publication No. 15. pp. 443-52. 1976).
[3]ICD9: International Classification of Diseases, Ninth Revision. World Health Organization, Geneva, 1977.
[4]Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

New Cancer Registrations

In the last decade, the number of new cases registered at the regional cancer centres and the OCI/PMH has increased by 47% from 15,114 cases to 22,214 (Table VIII). To assess the significance of these changes over time, one must take into account the introduction in 1979 of the *International Classification of Diseases, Ninth Revision*, which separated the categories -- in situ carcinoma and neoplasms of uncertain behaviour -- from malignant neoplasms. In addition, in 1981, the Foundation returned to the international practice of counting patients with skin cancer as having only two lesions -- basal-cell or squamous-cell cancer -- and not as having multiple cancers of the same histology in different body from malignant neoplasms. In addition, in 1981, the Foundation returned to the international practice of counting patients with skin cancer as having only two lesions -- basal-cell or squamous-cell cancer -- and not as having multiple cancers of the same histology in different body sites. The distribution by cancer centre of the numbers of in situ lesions, neoplasms of uncertain behaviour and multiple skin cancers is shown at the foot of Table IX.

This increase in the number of cases seen at the regional cancer centres can be attributed in part to the greater occurrence of cancer in the population during the last decade. This increase represents a combination of an increase in population in Ontario, which is also aging, and an increase in smoking-related cancers. It is anticipated that these trends will continue, with an expected annual increase in the absolute number of new cases of cancer requiring treatment.

In Table IX, for 1986, the major sites of newly registered cancers at these centres were lung, brochus and trachea (16%), and breast (17.6%), followed by non-melanoma of the skin (9.7%). Of the 20,295 cancers seen for the first time at one of the regional cancer centres or the OCI/PMH, 16.1% were seen in Hamilton, 5.4% in Kingston, 12.7% in London, 13.4% in Ottawa, 1.4 in Sudbury, 2.4% in Thunder Bay, 12.3% at Toronto-Bayview, 4.7% in Windsor, and 31.6% at the Princess Margaret Hospital.

It should be noted that a "new case" registered at a Foundation's regional cancer centre refers to a case of cancer seen for the first time during that year at any one of the Foundation centres. If a case is seen at two cancer centres in the same year, the case is recorded as seen only by the first centre (1% of cases were seen at more than two centres in the same year).

The location of the peripheral clinics associated with the regional cancer centres and the OCI/PMH, and the type of outreach program, determine the referral pattern to each (Table X). Thus, in Lambton County, of the 318 cases resident in the county, 311 were referred to the London Centre and only a small number to other centres. On the other hand, in Halton County, of the 534 cases resident in that county, 288 were referred to the Hamilton Centre, 232 to OCI/PMH and 11 were referred to the Toronto-Bayview Centre. From the Province of Quebec, 461 residents were referred to Foundation centres; most

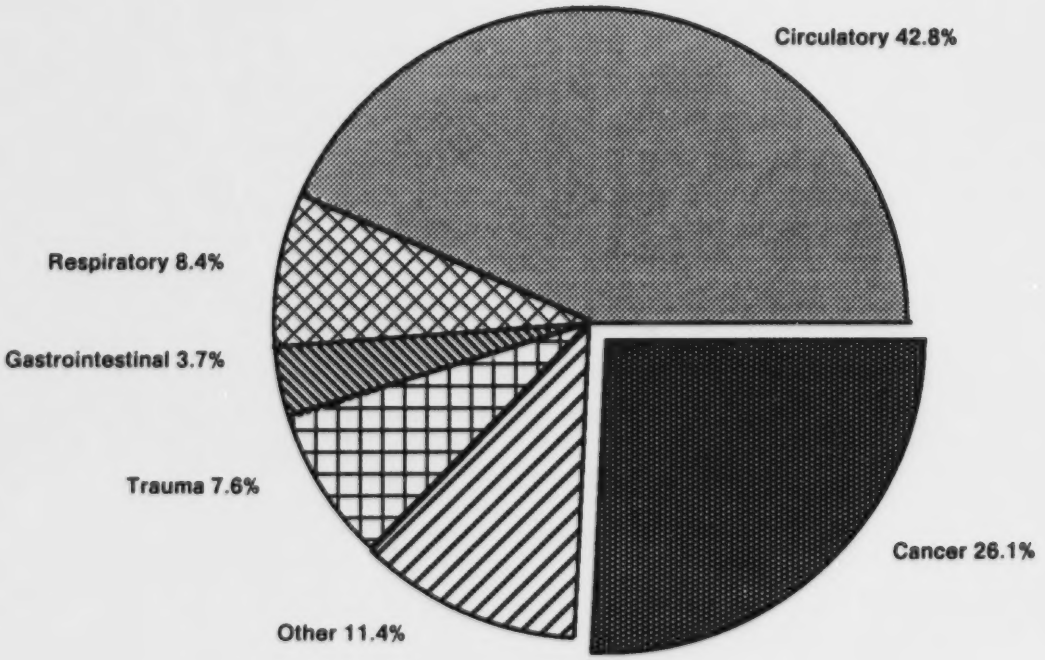

Fig. 2 Percentage distribution of major causes of death in males, Ontario 1986

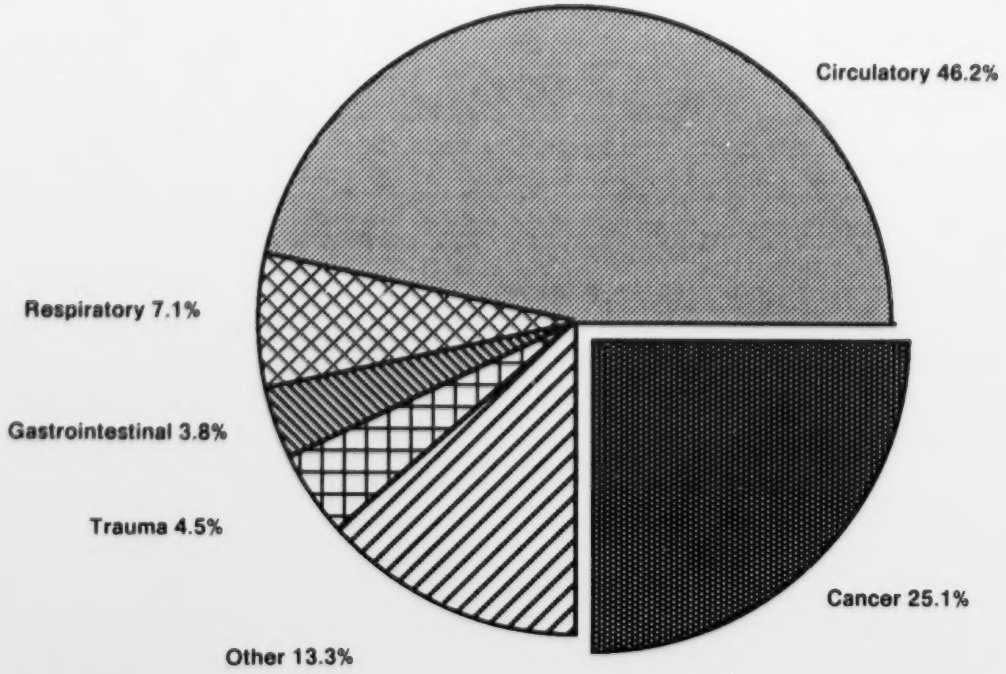

Fig. 3 Percentage distribution of major causes of death in females, Ontario 1986

TABLE V

Number of Deaths due to Malignant Neoplasms in Males, by Site of Disease and Age at Death, Ontario 1986

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	0	0	0	0	0	0	0	1	3	4	9	18	30	20	15	28	128	14.5
Pharynx	146-148	0	1	0	0	0	0	0	4	4	4	6	18	24	11	7	10	89	
Esophagus	150	0	0	0	0	0	0	0	0	2	12	24	35	52	42	26	55	248	9
Stomach	151	0	0	0	0	0	0	1	7	7	7	28	48	56	67	62	142	425	5
Intestine, except rectum	152,153	0	0	0	0	0	2	2	9	19	22	32	67	108	131	139	305	836	3
Rectum and anus	154	0	0	0	0	0	1	2	2	3	12	13	26	35	43	58	110	305	7
Pancreas	157	1	0	0	1	0	0	2	1	6	16	24	48	73	79	83	141	475	4
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	0	2	0	0	1	1	1	4	3	3	15	
Larynx	161	0	0	0	0	0	0	0	0	1	3	10	16	26	11	24	37	128	14.5
Trachea, bronchus and lung	162	0	0	0	0	0	0	2	17	32	85	156	335	515	540	506	775	2963	1
Bone	170	0	0	3	6	4	1	1	1	1	0	0	1	4	3	5	3	33	
Connective tissue	171	0	0	0	2	0	1	1	1	1	2	1	4	5	0	2	6	26	
Malignant melanoma of skin	172	0	0	0	0	2	4	6	14	5	13	4	9	9	11	15	18	110	16
Breast	175	0	0	0	0	1	0	0	0	0	0	0	1	3	0	0	3	8	
Prostate	185	0	0	0	0	0	0	0	0	0	1	7	34	65	99	176	529	911	2
Testis	186	0	0	0	0	1	1	2	2	1	2	0	1	1	0	0	0	11	
Bladder	188	0	0	0	0	0	0	0	2	0	2	5	12	27	44	46	128	266	8
Kidney and other urinary	189	0	0	0	0	0	0	2	1	6	9	21	22	36	42	30	55	224	12
Brain and other nervous system	191,192	3	4	1	1	4	8	9	9	16	21	21	35	37	35	13	26	243	11
Thyroid gland	193	0	0	0	0	0	0	0	0	0	1	1	3	2	3	1	2	13	
Lymphosarcoma and reticulosarcoma	200	0	0	0	2	1	1	2	3	3	2	6	4	7	13	9	22	75	
Hodgkin's disease	201	0	0	0	0	0	5	7	4	4	1	3	3	4	5	5	4	45	
Other lymphomas	202	0	0	0	0	2	1	3	7	6	6	21	21	30	39	39	69	244	10
Multiple myeloma	203	0	0	0	0	0	0	0	1	3	6	7	12	21	27	27	55	159	13
Leukemia	204-208	5	10	6	6	9	8	8	10	7	12	20	25	43	40	50	114	373	6
Other and non-specific	Residual	4	1	1	0	4	5	5	6	15	23	63	83	147	142	154	318	971	
TOTAL	140-208[3]	13	16	11	18	28	38	55	104	145	266	483	882	1,361	1,451	1,495	2,958	9,324	

[1]ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2]Rank order for sites with more than 100 deaths.
[3]Omitted are 42 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

TABLE VI

Number of Deaths due to Malignant Neoplasms in Females, by Site of Disease and Age at Death, Ontario 1986

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	0	0	0	0	0	0	0	0	2	1	2	9	10	7	7	21	59	
Pharynx	146-148	0	0	0	0	0	0	0	0	0	0	1	3	1	1	3	5	14	
Esophagus	150	0	0	0	0	0	0	0	0	0	3	3	10	18	12	13	50	109	16
Stomach	151	0	0	0	0	0	1	2	4	4	9	18	25	27	38	51	122	301	6
Intestine, except rectum	152,153	0	0	0	0	0	1	0	6	13	21	37	56	95	102	121	384	836	3
Rectum and anus	154	0	0	0	0	0	0	1	1	1	7	7	13	22	32	39	97	220	8
Pancreas	157	0	0	0	0	0	0	0	1	6	15	17	21	31	50	69	214	424	5
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	8	11	
Larynx	161	0	0	0	0	0	0	0	0	1	0	2	3	6	3	3	7	25	
Trachea, bronchus and lung	162	0	0	0	0	0	1	4	5	28	49	100	140	188	234	200	304	1253	2
Bone	170	0	0	1	0	2	2	0	0	0	0	0	0	1	4	0	3	13	
Connective tissue	171	1	2	0	1	1	0	0	1	1	3	2	3	2	1	5	5	28	
Malignant melanoma of skin	172	0	0	0	1	0	0	5	3	6	4	11	6	8	10	11	10	75	
Breast	174	0	0	0	0	1	5	17	63	79	109	162	179	237	171	194	471	1688	1
Cervix uteri	180	0	0	0	0	1	4	5	9	8	12	14	18	22	18	19	34	164	12
Other uterus	179,181,182	0	0	0	0	0	1	1	0	1	2	4	9	25	39	26	72	180	11
Ovary and fallopian tube	183	0	0	0	1	0	2	3	6	11	26	33	38	69	64	81	124	458	4
Bladder	188	0	0	0	0	0	0	1	0	1	1	1	5	7	11	16	69	112	15
Kidney and other urinary	189	0	0	0	0	0	0	0	3	1	3	7	9	23	13	19	57	135	14
Brain and other nervous system	191,192	4	4	0	1	1	6	10	3	6	4	23	22	27	33	34	40	218	9
Thyroid gland	193	0	0	0	0	0	0	1	0	0	0	1	1	3	2	6	11	25	
Lymphosarcoma and reticulosarcoma	200	0	1	0	1	0	0	1	1	1	1	6	8	9	8	13	19	69	
Hodgkin's disease	201	0	0	0	1	2	1	1	3	1	2	2	2	2	2	2	8	29	
Other lymphomas	202	0	0	1	1	0	2	1	3	4	8	10	17	20	24	30	69	190	10
Multiple myeloma	203	0	0	0	0	0	0	0	0	1	2	8	14	22	23	29	59	158	13
Leukemia	204-208	7	2	3	5	2	7	5	4	7	11	11	14	22	28	30	103	261	7
Other and non-specific	Residual	1	0	3	3	1	3	7	7	14	18	37	58	88	109	131	421	901	
TOTAL	140-208[3]	13	9	8	15	11	36	65	123	197	311	520	683	985	1,039	1,154	2,787	7,956	

[1]ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977
[2]Rank order for sites with more than 100 deaths
[3]Omitted are 16 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

TABLE VII

World Standard Population and Estimated Population 1985 and 1986, of Ontario (In Thousands)

AGE GROUP	WORLD STANDARD[1]	ONTARIO, 1985[2]		ONTARIO, 1986[2]	
	MALE OR FEMALE	MALE	FEMALE	MALE	FEMALE
0-4	12.0	322.8	308.5	323.3	308.1
5-9	10.0	309.2	295.1	311.4	296.8
10-14	9.0	331.8	313.5	323.5	306.3
15-19	9.0	359.7	342.3	352.7	336.4
20-24	8.0	429.4	418.8	408.6	406.0
25-29	8.0	395.1	404.9	406.5	414.6
30-34	6.0	365.4	381.4	372.3	389.6
35-39	6.0	354.1	359.1	362.1	370.2
40-44	6.0	283.8	282.1	292.4	292.3
45-49	6.0	242.7	241.3	244.6	244.1
50-54	5.0	234.4	232.4	231.3	230.1
55-59	4.0	225.2	233.3	226.1	229.7
60-64	4.0	201.2	227.1	202.0	227.9
65-69	3.0	145.9	172.5	151.8	181.9
70-74	2.0	117.8	149.8	118.1	150.8
75+	2.0	139.0	246.4	140.9	249.1
TOTAL	100.0	4,457.5	4,608.5	4,467.6	4,633.9

[1] Waterhouse, John et al (eds): Cancer Incidence in Five Continents, Vol IV. World Health Organization, Geneva, 1982, p.673.
[2] Source: Statistics Canada.

TABLE VIII*

New Cancer Cases Registered by Treatment Centre, 1977-1986[1,2]

CENTRE	YEAR OF REGISTRATION									
	1977	1978	1979	1980	1981	1982*	1983	1984	1985	1986
Hamilton	2,353	2,493	2,594	2,507	2,537	2,688	2,780	2,782	3,498	3,472
Kingston	988	1,040	999	984	997	1,073	1,226	1,195	1,238	1,316
London	2,344	2,488	2,537	2,583	2,529	2,563	2,748	2,950	3,080	3,011
Ottawa	1,759	1,902	1,997	2,078	2,190	2,248	2,573	2,847	2,929	2,963
Sudbury	–	–	–	–	–	–	–	–	–	285
Thunder Bay	365	412	369	401	462	444	435	506	505	513
Toronto-Bayview	–	–	–	441	504	816	1,251	1,826	2,264	2,774
Toronto, PMH	6,462	6,960	6,911	7,057	7,320	7,012	7,332	7,171	7,328	6,840
Windsor	843	854	898	813	907	858	960	1,038	1,053	1,096
TOTAL	15,114	16,149	16,305	16,864	17,446	17,702	19,305	20,315	21,895	22,214

*Provisional (transition period – see text)
[1] Excludes carcinoma of cervix in situ.
[2] Any case registered at more than one treatment centre in a given year is allocated to the centre where it was first registered.

TABLE IX

New Cancer Cases Registered by Site of Disease and Treatment Centre, 1986

SITE OF DISEASE	ICD9[1] NUMBER	TREATMENT CENTRE									TOTAL	
		Hamilton	Kingston	London	Ottawa	Sudbury	Thunder Bay	Toronto		Windsor	Number	Per Cent
								Bayview	PMH			
Lip	*140	6	6	21	6	0	3	10	23	4	79	0.4
Tongue	*141	22	2	28	25	0	2	17	79	5	180	0.9
Rest of mouth	142-145	44	12	35	41	3	5	35	130	17	322	1.6
Pharynx and tonsil	146-149	35	10	36	42	2	4	32	131	13	305	1.5
Esophagus	*150	33	12	32	28	4	7	36	89	3	244	1.2
Stomach	*151	42	7	21	47	4	7	29	58	18	233	1.1
Intestine, except rectum	152.153	117	39	101	154	14	19	82	210	59	795	3.9
Rectum and anal canal	*154	120	39	80	102	5	16	65	291	36	754	3.7
Other digestive system	155-159	51	12	46	63	7	16	35	63	32	325	1.6
Nose, middle ear and accessory sinuses	*160	10	2	5	8	2	1	5	27	0	60	0.3
Larynx	*161	48	16	57	65	1	16	51	180	14	448	2.2
Lung, bronchus and trachea	*162	481	220	424	448	36	71	468	922	167	3,237	16.0
Other respiratory	163-165	9	5	8	11	2	1	10	24	4	74	0.4
Bone	*170	7	2	11	10	2	2	13	17	2	66	0.3
Malignant melanoma	*172	104	27	48	68	6	8	163	133	26	583	2.9
Other cancer of skin	*173	306	182	295	186	1	40	376	475	116	1,977	9.7
Breast	174,175	540	163	473	497	70	84	394	1,186	160	3,567	17.6
Cervix uteri	*180	68	27	45	62	6	10	31	211	7	467	2.3
Other uterus	179,181,182	129	27	78	106	6	10	31	207	27	621	3.1
Ovary, tubes and ligament	*183	82	13	51	58	8	11	29	171	13	436	2.1
Other female genital organs	*184	20	4	20	17	1	1	8	40	2	113	0.6
Prostate	*185	151	62	118	124	26	25	139	290	36	971	4.8
Testis	*186	23	14	16	29	0	3	19	98	7	209	1.0
Other male genital organs	*187	1	0	4	2	0	1	2	7	1	18	0.1
Bladder	*188	97	20	44	66	3	5	37	128	21	421	2.1
Kidney and other urinary	*189	40	12	38	46	2	12	29	74	15	268	1.3
Brain and nervous system	191,192	79	17	82	62	3	5	79	131	19	477	2.4
Thyroid gland	*193	10	1	8	7	2	2	[illegible]	55	4	91	0.4
Lymphosarcoma and reticulum-cell sarcoma	*200	43	20	57	54	18	16	38	192	14	452	2.2
Hodgkin's disease	*201	40	11	27	35	8	13	31	101	11	277	1.4
Other lymphomas	*202	97	21	45	57	6	13	37	98	16	390	1.9
Leukemia	204-208	87	37	55	48	8	16	39	143	42	475	2.3
Other sites	Residual	320	44	175	151	23	43	123	428	53	1,360	6.7
TOTAL MALIGNANT		3,262	1,086	2,584	2,725	279	488	2,495	6,412	964	20,295	100.0
Cervix uteri (in situ)	*233.1	5	1	2	8	2	0	1	12	0	31	...
Other sites (in situ)	230-234	44	20	48	43	2	6	99	80	23	365	...
Neoplasms of uncertain behaviour	235-238	24	13	31	15	3	6	16	58	12	178	...
Multiple skins (see text)	*173	142	197	348	180	1	13	164	290	96	1,431	...
Seen at more than one centre		6	24	23	23	0	1	11	106	8	202	

*Provisional (transition period – see text)

[1]ICD9 – International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

TABLE X

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1986

COUNTY OR DISTRICT	TREATMENT CENTRE									TOTAL
	Hamilton	Kingston	London	Ottawa	Sudbury	Thunder Bay	Toronto		Windsor	
							Bayview	PMH		
Algoma	3	1	5	2	8	2	6	132	2	161
Brant	220	–	14	–	–	–	2	8	–	244
Bruce	2	1	98	–	–	–	2	38	–	141
Carleton	3	2	2	1,391	–	–	12	10	–	1,420
Cochrane	5	–	6	22	1	8	4	109	1	156
Dufferin	1	–	1	–	–	–	6	34	–	42
Dundas	–	1	–	36	–	–	–	–	–	37
Durham[2]	2	–	1	1	–	–	92	357	–	453
Elgin	–	–	167	–	–	–	1	1	–	169
Essex	3	–	63	–	–	–	6	8	892	972
Frontenac	–	324	–	3	–	–	2	5	–	334
Glengarry	–	1	–	58	–	–	1	–	–	60
Grenville	–	33	–	30	–	–	1	–	–	64
Grey	8	1	71	–	–	–	13	106	–	199
Haldimand-Norfolk[3]	155	–	57	2	–	–	–	6	1	221
Haliburton	–	1	–	–	–	–	3	31	–	35
Halton	288	–	2	1	–	–	11	232	–	534
Hastings	1	223	–	15	–	–	23	64	–	326
Huron	–	–	123	–	–	–	3	2	–	128
Kenora	–	2	1	2	–	36	–	5	–	46
Kent	–	–	222	–	–	–	–	4	20	246
Lambton	–	1	311	1	–	–	3	1	1	318
Lanark	–	31	–	101	–	–	1	2	–	135
Leeds	1	148	–	12	–	–	2	5	–	168
Lennox and Addington	–	89	–	4	–	–	1	8	1	103
Manitoulin	–	–	1	–	9	–	1	12	–	23
Middlesex	1	–	804	1	–	–	–	8	2	816
Muskoka	2	1	2	–	–	–	15	93	–	113
Niagara[1]	802	–	2	2	1	–	21	90	–	918
Nipissing	3	1	1	8	5	–	3	169	–	190
Northumberland[2]	–	20	1	2	–	–	30	116	–	169
Oxford	2	–	203	–	–	–	–	3	–	208
Parry Sound	1	–	3	2	1	–	11	63	–	81
Peel	12	1	1	1	1	–	113	629	2	760
Perth	–	–	119	1	–	–	1	1	–	122

TABLE X (Continued)

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1986

COUNTY OR DISTRICT	TREATMENT CENTRE									TOTAL
	Hamilton	Kingston	London	Ottawa	Sudbury	Thunder Bay	Toronto		Windsor	
							Bayview	PMH		
Peterborough[2]	5	4	1	–	–	–	37	189	–	236
Prescott	–	–	–	67	–	–	–	1	–	68
Prince Edward	1	51	1	–	–	–	8	7	–	68
Rainy River	–	–	–	–	–	36	–	1	–	37
Renfrew	–	4	–	252	–	–	1	1	–	258
Russell	1	–	–	34	–	–	–	–	–	35
Simcoe[2]	4	–	1	1	–	–	123	325	–	454
Stormont	3	8	–	160	–	–	–	5	–	176
Sudbury	1	–	5	12	234	1	15	205	3	476
Thunder Bay	8	–	3	–	1	403	3	19	2	439
Timiskaming	–	–	5	3	7	–	11	56	–	82
Victoria[2]	1	–	–	–	–	–	27	82	–	110
Waterloo	176	–	231	1	1	–	7	60	2	478
Wellington	173	–	34	1	–	–	12	35	–	255
Wentworth	1,065	1	1	1	–	–	6	8	1	1,083
York	8	8	6	5	–	–	1,658	2,919	3	4,607
Quebec	2	6	–	427	–	1	4	21	–	461
Other Provinces	7	7	5	29	2	1	13	71	6	141
U.S.A.	3	14	7	7	3	–	5	12	14	65
Other World	–	1	1	14	1	–	15	40	2	74
Residence at diagnosis not stated	289	100	2	13	4	–	160	3	9	580
TOTAL	3,262	1,086	2,584	2,725	279	488	2,495	6,412	964	20,295

[1] In 1971 the counties of Welland and Lincoln became the Regional Municipality of Niagara.
[2] In 1974 the counties of Durham and Ontario became the Durham Regional Municipality. Also the counties of Simcoe, Peterborough, Northumberland and Victoria have been expanded by parts of Durham and Ontario.
[3] In 1974 the counties of Haldimand and Norfolk became the Regional Municipality of Haldimand-Norfolk.

were seen at the Ottawa Centre. Additional 141 residents of other provinces were seen in Ontario, principally at the OCI/PMH. Of the 139 residents of the USA and other countries treated in Ontario, most were seen at the OCI/PMH, and the Toronto-Bayview and Ottawa Centres.

The data in Tables VIII-X were extracted from the centres in September or October 1987. Data extracted later may differ slightly from those presented here.

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APPENDICES

APPENDIX A

BEQUESTS AND OTHER DONATIONS

The Foundation was the grateful recipient of legacies, bequests and other donations totalling $1,606,082 for the fiscal year ending March 31, 1987, which are of inestimable value to the Foundation's program.

Legacies of $1,000 or over were received during the above period from the following estates:

The late Frederick James Arthurs, Ottawa	$102,151
— Mary Bieniewski, Toronto	50,000
— Emma May Bradt, Aylmer for research at London Centre	8,628
— Jennie Breindahl, Ottawa for use at Ottawa Centre	45,000
— Ethel Bremner, Toronto for research	26,918
— Isabella Campbell, Ottawa	1,000
— Eileen Victoria Carey, Goderich	17,000
— George Hilbert Cline, Stoney Creek	12,272
— Arthur Grafton, Collamore, Lambeth for use at London Centre	10,143
— Mary Cooke, Windsor for construction at Windsor Centre	265,835
— Edna Maude Victoria Crosbie, Toronto for research	38,269
— John Canham Dale, Harriston for use at London Centre	1,000
— Norma Melville Deavitt, Township of Georgina	9,470
— Beecher Dennis, Toronto	32,989
— Dorothy Dodds, Perth for research	2,000
— Eldred Durham, Toronto (Anne and Eldred Durham Trust Fund) for research	15,692
— Viola Franklin, London	5,000
— John Jacob Freedman, Toronto	10,000
— Harold Gallagher, London for use at London Centre	5,000

– Gertrude L. Garbutt, Toronto	50,000
– Gordon C. Garbutt, Toronto	65,000
– Hazel Norma Gilbert, London	7,000
– Erma Zoe Louise Goering, Hamilton for research at Hamilton Centre	8,000
– Mary Marguerite Harbour, Etobicoke	45,000
– William Hirsch, North York	28,589
– Ethel Ellen Hooker, Toronto	1,000
– Martha M. Jefferson, Ottawa for use at Ottawa Centre	1,000
– Mabel Matilda Kelley, London for use at London Centre	37,500
– Mary Helen Kirkpatrick, Scarborough	21,397
– Lorenz Philip Conrad Koehler, London for research at London Centre	2,127
– Dorothy Kruger, Ottawa for use at Ottawa Centre	10,000
– Verna Marguerite Logan, St. Marys for use at London Centre	2,000
– Edna Doris Lowe, Toronto	1,583
– Henry E.B. Mitchell, London for use at London Centre	10,000
– Vera Victoria Morrison, Scarborough	1,000
– Robert McBride, Hamilton	45,000
– Robert Sutherland McDonald, Toronto	10,304
– Clara B. Oliver, Ailsa Craig for research at London Centre	1,000
– Editha Reisgen, London for research at London Centre	8,057
– Agnes J. Richardson, London for research at London Centre	2,000
– Bertha Mabel Richter, London (Richter Endowment Fund Trust) for use at London Centre	154,000
– Clara Bell Sanderson, Brandford	8,775
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– Gladys Smith, Toronto	3,300
– Violet Beatrice Stewart, London for research at London Centre	1,000
– George W. Suggitt, Toronto	1,000
– Elizabeth Taylor, Orillia	2,466
– Lovena Mary Estella Taylor, Orangeville	1,000
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— Madeleine Wilson, St. Marys
for research at London Centre 37,728
— Mabel Irene Wright, Willowdale
for research 3,586

Donations of $1,000 or more were received from the following:
— Louis Aldrovandi, Woodbridge
for purchase of Pain Pump
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— Mark and Joan Aldrovandi, Willowdale
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— Barrhaven Lioness Club, Nepean
for hyperthermia use at Ottawa Centre 1,027
— Barrhaven Lions Club, Nepean
for hyperthermia research
at Ottawa Centre 1,500
— Brenda Bigelow, Don Mills
for use at Toronto-Bayview Centre 3,000
— Irene Boulton, Windsor
for research at Windsor Centre 1,000
— Canadian Cancer Society
Ontario Division, Toronto
for therapy equipment at
Windsor Centre ..... U.S. 7,057
— James Dennett, Corunna
for research at London Centre 1,000
— Richard Devarennes, Fergus
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— East London Minor Athletic Association, London
for use at London Centre 3,200
— Feldman Windows Mfg. Ltd., Tilbury
for construction of bunker building
at Windsor Centre 1,364
— IBM Canada Ltd., Markham
for hyperthermia use
at Ottawa Centre 10,000
— Knights of Columbus, Windsor
St. Clement's Council No. 2844
for building fund at Windsor Centre 10,000

– Lakehead Shrine Motor Patrol, Thunder Bay	
for use at Thunder Bay Centre	1,500
for purchase of two infusion pumps at Thunder Bay Centre	1,500
– Arthur H. Lang, Ottawa	
for use at Ottawa Centre	1,000
– William H. Lavery, Toronto	
in memory of Jean S. Galbraith	1,000
– Leaker Mushrooms Co., Ltd., Campbellville	
in memory of John LaPorte	
for equipment at Toronto-Bayview Centre	1,000
– Dr. P.C. MacEwen, Ottawa	
for hyperthermia research at Ottawa Centre	1,033
– Employees of the Oshawa Group Ltd., Toronto	1,688
– Ottawa Civic Hospital Foundation, Ottawa	
for hyperthermia research at Ottawa Centre	2,928
for psychosocial research at Ottawa Centre	29,314
– The Mario and Antonia Paolucci Charitable Foundation, Willowdale	
for research	1,500
for treatment	500
– Poplar Grove Golf Club, R.R. 2, Edwards	
for use at Ottawa Centre	1,000
– Paul and Vicki Ronco, West Hill	
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– Employees of the Royal Bank of Canada, Toronto	2,176
– Stelco War Veterans' Association, Hamilton	
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– Ila M. Stewart, London	
for use at London Centre	10,000
– Stewart, Young & Mason Ltd., Toronto	
in memory of David Mason	1,000
– Robert J. Tebbs, Windsor	
for research at Windsor Centre	5,000
– Tessier, Knox & Associates Ltd., Aurora	
for use at Toronto-Bayview Centre	1,000
– Texaco Canada Inc., Don Mills	
for research	4,000
– Thunder Bay Foundation, Thunder Bay	
for pastoral care services at Thunder Bay Centre	1,900

– William S. Tomlinson, Thunder Bay for equipment at Thunder Bay Centre	5,000
– Harold Wrigglesworth, Don Mills (Dorothy Wrigglesworth Cancer Research Fund)	1,000

The Foundation is grateful to these donors and to the many others not listed above and it reveres the memory of those who, when making their wills, extended beyond their lifetime fight against cancer. These welcome additions to our research program and other funds ensure that the Foundation's extensive research program can proceed at a time of financial constraints and inflated costs.

APPENDIX B

LIST OF ARTICLES PUBLISHED IN 1986 BY CAREER SCIENTISTS, RESEARCH ASSOCIATES GRANTEES, MEMBERS OF THE OCTRF STAFFS AT THE REGIONAL CANCER CENTRES AND HEAD OFFICE AND THE OCI/PMH

HAMILTON

OCTRF Hamilton Regional Cancer Centre:

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KINGSTON

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